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The American Heart Journal

VOL. 20 JULY, 1940 NO. 1

Original Communications

IMMUNIZATION AGAINST RHEUMATIC FEVER WITH HEMOLYTIC STREPTOCOCCUS FILTRATE

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NEW YORK, N. Y.

IN A PREVIOUS publication,* one of us discussed the effect on thirty-four patients known to have rheumatic fever of immunization with the filtrate of N. Y. 5 hemolytic streptococcus. The results showed that during the four years of therapy 5.9 per cent of the patients suffered attacks of acute rheumatic fever with or without carditis, whereas the two control groups during the same period showed an incidence of 15 per cent and 43.4 per cent, respectively.

The results were so encouraging that we undertook the immunization of another group of children, selected at random from the Cardiac Clinic.† During the two years of treatment on which we are now reporting, two groups of patients served as controls, one for each year.

In addition, one of us has re-examined the patients discussed in the previous article,‡ both treated and untreated, after the lapse of two years without further therapy, and the report on their condition will be found at the end of this article.

This paper deals primarily with the immunization of thirty-two new patients, from October, 1937, to June, 1939. During the first winter (1937-38), forty-one patients were used as controls, and, during the second winter, thirty-nine. Both the treated and the control patients were examined periodically at the Cardiac Clinic.

The only criteria for selecting the patients for treatment were their early enrollment for immunization (September and October) and their promise to cooperate during the protracted course of inoculations, which required, at first, weekly, and then monthly, visits to the clinic each winter, amounting to a total of from thirty-four to thirty-six visits.

*Wasson, V. P.: Immunization Against Rheumatic Fever With Hemolytic Streptococcus Filtrate, AM. HEART J. 15: 257, 1938.

†From the Department of Pediatrics, New York Post-Graduate Hospital and Medical School.

‡Through the courtesy of the Flower-Fifth Avenue Hospital, New York City.

Received for publication Nov. 4, 1939.

The reader is referred to the previous paper, mentioned above, for a detailed account of the preparation of the filtrate and method of administration.

The control group was made up of patients who presented themselves after the enrollment of the treated group was completed, or of those whose parents could not or would not bring them to the clinic regularly.

The cooperation of the treated patients was very good. Of the thirty-two treated children, only one dropped out; his record ends with the first year. The untreated patients were naturally less interested in regular attendance. Of the forty-one patients in the first year control group, only nineteen were carried over into the second year, and the rest of the 1938-39 control group was made up of newcomers in the fall of 1938.

About one-third of the patients were Italians, about one-third Jews, and the rest were mostly of Irish and Anglo-Saxon stock. Their economic and educational status was higher than that of the patients described in 1938.

The routine procedure with each treated and untreated patient was the same. On admission to the rheumatic research clinic a careful history was taken, with special emphasis on familial, racial, and hygienic factors. An inquiry was made into the child's habits, school career, and emotional make-up.

As a rule, each patient was examined carefully at the outset in the Cardiac Clinic; the examination included an exercise tolerance test, a teleoroentgenogram, and an electrocardiogram. Since most of the rheumatic fever patients suffer from chronic sinusitis, the nasopharynx received special attention from one of us. Next followed the laboratory procedure, which consisted, at the start, of a routine urinalysis, a complete blood count, with special emphasis on the nonfilamented neutrophil (Schilling) count, and the erythrocyte sedimentation rate. As to the latter, in the clinic we used only Landau's microsedimentation technique.* The Social Service Department generously helped whenever necessary. The patients' parents were given printed instructions, telling in simple language how to deal with children suffering from rheumatic fever.

At each subsequent visit we took the interval history, did a Schilling count, and measured the hemoglobin percentage and the erythrocyte sedimentation rate. If the patient showed symptoms of subacute rheumatic fever or a severe upper respiratory infection, he was sent home to bed, with instructions to return in three to seven days. In case of an acute attack of rheumatic fever, as diagnosed by us and the Cardiac Clinic, the patient, as a rule, was admitted to the hospital or visited at home by one of the cardiologists.

*Normal high value is 10 mm. per hour.

In this paper the clinical and laboratory observations were taken wholly from ambulatory patients, in order to exclude all data not accumulated at the clinic by us and by the same laboratory technicians.

As not all of the control patients were the same during the first and second years of observation, it is necessary to present separately

TABLE I

COMPARISON OF TREATED AND CONTROL GROUPS

		FIRST YEAR		
		TREATED		CONTROL
Number of Patients		32		41
Average Age		12.9		9
Sex	Males	19	Males	17
	Females	13	Females	24
Cardiac Class	F	4	F	4
	E + F	7	E + F	12
	I	12	I	11
	IIA	8	IIA	11
	IIB	1	IIB	3
No. of Colds per Child		2.6		1.8
Average Gain in Weight		5 lb.		3.5 lb.
Abdominal Symptoms		10+		13+
		1++		1++
		3+++		4+++
Pallor		4+		8+
		3++		2++
		4+++		12+++
Epistaxis		5+		6+
				4++
		3+++		3+++
Rheumatic Pains		5+		6+
		7++		4++
		3+++		18+++
Cardiac Symptoms		2+		5+
		1++		4++
		1+++		11+++
Headaches		4+		10+
				4++
		7+++		9+++
Twitching		2+		3+
				2++
				5+++
Severe Infections		2 Otitis Media		
No. of Attacks of Acute Rheumatic Fever, Carditis, and Chorea		3 (9.37 per cent)		18 (44 per cent)
Average E. S. R.		9.5 mm. per hr.		14 mm. per hr.
Average Hemoglobin		77.4 per cent		75 per cent
Average Nonfilamented Count		8 cells per 100		11.8 cells per 100
Results:	Excellent	7 (22 per cent)		7 (17 per cent)
	Very Good	9 (28 per cent)		3 (7 per cent)
	Good	5 (15.7 per cent)		5 (12.2 per cent)
	Average	4 (12.5 per cent)		7 (17 per cent)
	Fair	4 (12.5 per cent)		1 (2.44 per cent)
	Poor	3 (9.37 per cent)		18 (44 per cent)

Symbols: + occurred once.
++ occurred twice.
+++ occurred several times.

the comparisons of the treated and the untreated patients for each year. This division by years also shows more clearly the progress of the treated patients. The results are presented in Tables I and II.

TABLE II

COMPARISON OF TREATED AND CONTROL GROUPS

		SECOND YEAR		
		TREATED		CONTROL
Number of Patients		31		39
Average Age		13.9		11
Sex	Males	18	Males	17
	Females	13	Females	22
Cardiac Class	F	4	F	1
	E + F	8	E + F	12
	I	14	I	10
	IIA	5	IIA	13
	IIB	1	IIB	3
No. of Colds per Child		2.4		3
Average Gain in Weight		8.72 lb.		6.1 lb.
Abdominal Symptoms		8+		10+
		3++		5++
				4+++
Pallor		5+		4+
		2++		6++
		1+++		14+++
Epistaxis		4+		10+
		2++		2++
		1+++		4+++
Rheumatic Pains		5+		5+
		5++		4++
		2+++		14+++
Cardiac Symptoms		1+		5+
		1++		3++
				9+++
Headaches		5+		5+
		4++		4++
		2+++		12+++
Twitching		0		1+
				1++
				4+++
No. of Attacks of Acute Rheumatic Fever, Chorea, and Carditis		1 (3.2 per cent)		11 (28.2 per cent)
Average E. S. R.		6.9 mm. per hr.		10 mm. per hr.
Average Hemoglobin		75.37 per cent		72.4 per cent
Average Nonfilamented Count		6.6 cells per 100		8.3 cells per 100
Results:	Excellent	14 (45.1 per cent)		8 (20.51 per cent)
	Very Good	8 (26 per cent)		7 (17.92 per cent)
	Good	5 (16 per cent)		4 (10.26 per cent)
	Average	2 (6.4 per cent)		6 (15.36 per cent)
	Fair	1 (3.2 per cent)		3 (7.68 per cent)
	Poor	1 (3.2 per cent)		11 (28.20 per cent)

Symbols: + occurred once.
++ occurred twice.
+++ occurred several times.

DISCUSSION OF TABLES

The Treated Group, between October, 1937, and June, 1938, was made up of thirty-two patients. Their average age at the outset of treatment was 12.9 years. Among them there were nineteen males and thirteen females. Eight fell in Class IIA, and one in IIB.

During the first year of treatment the average sedimentation rate was 9.5 mm. per hour, the hemoglobin, 77.4 per cent, and the Schilling, or nonfilamented, cell count, 8 cells per 100. There was an average of 2.6 colds per child. Two cases of acute exacerbation of chronic otitis media occurred, and three children, or 9.4 per cent of the treated children, suffered attacks of acute rheumatic fever, carditis, and chorea. The average gain in weight from October to June was five pounds.

Among the major subacute rheumatic fever symptoms the following occurred more than twice during the first winter: abdominal pain in three children, pallor in four, epistaxis in three, precordial pain and dyspnea in one, and headaches in seven. Mild twitchings were observed in two children at the outset of treatment.

Control Group, First Year.—Forty-one children made up the control group in 1937-38. The average age at the time of their enrollment was 9. Seventeen of the patients were boys, and twenty-four were girls. When first admitted to the group, eleven children were in cardiac Class IIA, and three in IIB. The average erythrocyte sedimentation rate, hemoglobin percentage, and nonfilament count were 14 mm. per hour, 75 per cent, and 11.8 cells, respectively. The average number of reported colds was only 1.8 per child. The average gain in weight from October until June was 3.5 pounds. Eighteen out of forty-one children suffered from attacks of acute rheumatic fever, an incidence of 44 per cent.

The subacute rheumatic symptoms were also prominent. Among the cardinal symptoms which occurred on more than two occasions were: abdominal symptoms in four patients, pallor in twelve, epistaxis in three, joint and muscle pains in eighteen, dyspnea and precordial pains in eleven, headaches in nine, and chorea in five.

The results of the second year of treatment may be summarized as follows:

Treated Group, Second Year.—At the end of the first year one patient drifted away, and observations on only thirty-one patients are available for 1938-39. Of the eight Class IIA patients in the first year, only five started as such in the second year; two had passed into Class I, and the eighth was the patient who was lost sight of. The gain in weight was 8.7 pounds per child for the twelve months. The average erythrocyte sedimentation rate was 6.9 mm. per hour, the hemoglobin, 75.3 per cent, and the nonfilament count, 6.6 per cent. There was only one attack of acute rheumatic fever, an incidence of 3.2 per cent, and the

number of upper respiratory infections per child was 2.4. All of the subacute rheumatic symptoms abated markedly. Not one patient complained of frequent abdominal or cardiac symptoms. One child remained chronically pale. One had more than two nosebleeds, two reported joint pains more than twice, and two reported frequent headaches.

Control Group, Second Year.—Among the thirty-nine children observed during the winter of 1938-39, there were seventeen females and twenty-two males. Of the thirty-nine, thirteen belonged to cardiac Class IIA, and three to IIB. The average age was 11 years, and the average gain in weight was 6.1 pounds for the twelve months. The erythrocyte sedimentation rate per child was 10 mm. per hour, the hemoglobin percentage, 72.4, and the nonfilamented count, 8.3 cells. There were three colds per child, and eleven attacks of acute rheumatic fever, chorea, and carditis in the group. Most of the eleven were hospitalized. The subacute rheumatic symptoms were many and troublesome. Among the complaints which occurred on more than two occasions there were abdominal symptoms in four, chronic pallor in fourteen, precordial pain and dyspnea in nine, epistaxis in four, joint and muscle pains in fourteen, headaches in twelve, and chorea in four.

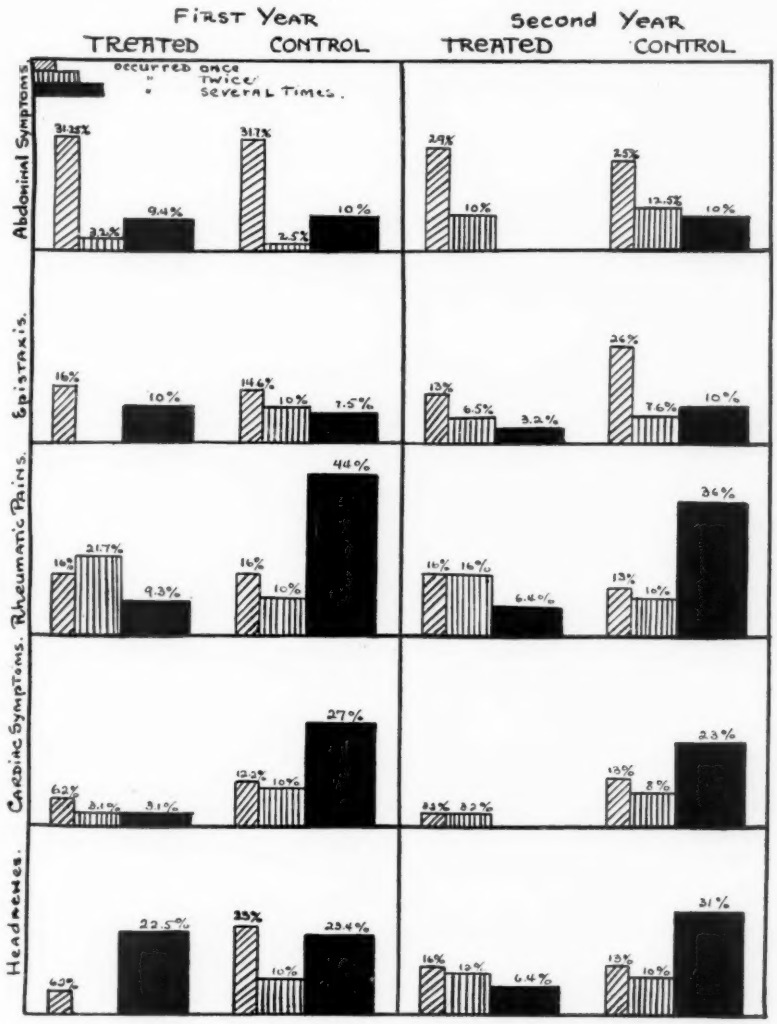
Tables I and II give our estimate of the child's health, not only from the point of view of rheumatic fever, but also by accepted health standards. In the category "Excellent," we place children who, apart from one or two transitory colds, presented no complaints and have led a normal life. Under "Very Good," we put children who had not more than one complaint, apart from usual upper respiratory infections; under "Good," those who maintained better than average good health, but could improve further. Under the term "Average," we placed children who were not really sick, yet never "really well"; under "Fair," those who were in a state of chronic ill-health, yet escaped acute illness. By "Poor," we mean all those who suffered attacks of acute rheumatic fever, as diagnosed by us and corroborated by the cardiologists. Although these categories may appear at first somewhat indeterminate, they are merely a conclusion derived from the tabulated clinical and laboratory evidence.

In Graph I we show the occurrence of common rheumatic symptoms in treated and control patients.

In our opinion, two of the most important laboratory aids in the detection of rheumatic activity are the erythrocyte sedimentation rate and the Schilling count. We found during the first year that the two tests kept in step with each other in 79 per cent of our cases. In Graph IIA we have plotted the average weekly values of the erythrocyte sedimentation rate and the nonfilamented cell counts for the two consecutive winters. From ten to forty estimations were made in each case, so that the curve gives a fair picture of the variations.

Graph II*A* shows, first, the seasonal rise and fall in rheumatic activity; second, the parallel tendency that exists between fluctuations of the erythrocyte sedimentation rate and the nonfilament count (both high normal values being taken as ten); third, the lower incidence of abnormal sedimentation rates and nonfilamented cells in the treated, as compared with the untreated, groups; and, fourth, the gradual improvement in the treated patients in the course of therapy.

Graphs II*B* and II*C* are presented to elucidate and support Graph II*A*. They show the weekly values for individual patients, one graph for the treated patients and the other for the untreated.



Graph I.—Graphic presentation of five common symptoms of rheumatic fever that occurred in treated and control patients, October, 1937, to June, 1939.

FOLLOW-UP ON FORMERLY TREATED PATIENTS

It was obviously of great interest to us to know how the patients reported in the previous paper on this subject* had fared since the treatment was discontinued, in June, 1937. The Flower-Fifth Avenue Hospital gave one of us the facilities for looking up all of the patients, treated and controls, and the results of this investigation are presented in Table III.

TABLE III

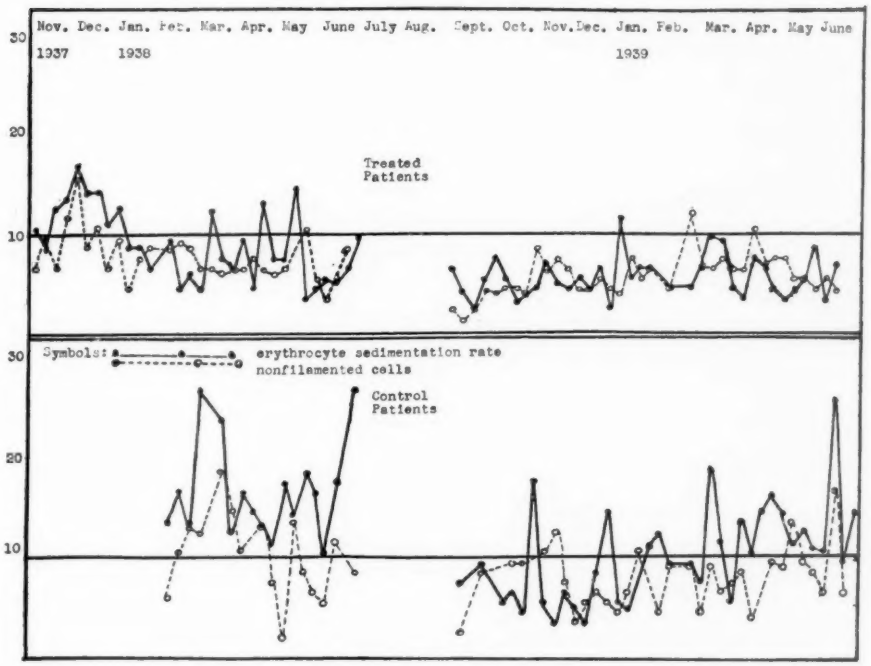
TWO-YEAR FOLLOW-UP OF PATIENTS AT THE FLOWER-FIFTH AVENUE HOSPITAL

	TREATED	CONTROLS
	BETWEEN 1933 AND 1937	
No. of Patients Followed Up	29 out of 33	30 out of 32
Seen Personally	25	22
Seen Records	4	8
Average Age When Followed Up	12	12.6
Sex Males	15	Males 16
Females	14	Females 15
Average Gain in Weight	20.6 lb.	15.4 lb.
Colds, Per Child	1.8	3
Abdominal Symptoms	2+	4+
	1++	4++
	1+++	6+++
Cardiac Symptoms	2+	1+
	0	1++
	2+++	8+++
Headaches	5+	1+
	0	1++
	1+++	7+++
Epistaxis	0	4+
	1++	2++
	1+++	2+++
Rheumatic Pains	5+	3+
	1++	2++
	2+++	13+++
No. of Attacks of Acute Rheumatic Fever, Carditis, and Chorea	2 (7 per cent)	10 (33 per cent) (1 death)
Results: Excellent	17 (58 per cent)	9 (30 per cent)
Very Good	7 (24 per cent)	0
Good	2 (6.9 per cent)	1 (3.3 per cent)
Average	1 (3.5 per cent)	4 (13.2 per cent)
Fair	0	6 (19.8 per cent)
Poor	2 (7 per cent)	9 (30 per cent)
Death		1 (3.3 per cent)

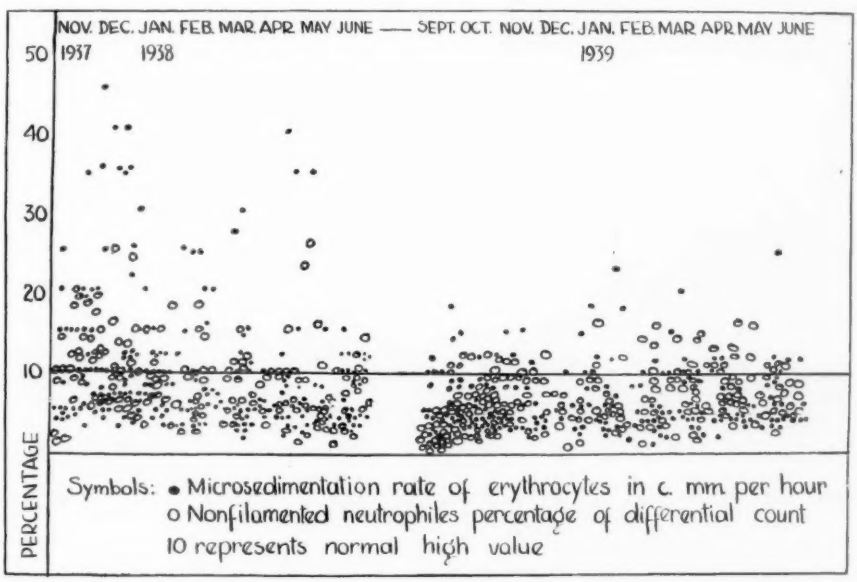
Symbols: + occurred once.
++ occurred twice.
+++ occurred several times.

We were successful in getting data on twenty-nine out of thirty-three treated children, and on thirty out of thirty-two controls. Of the previously treated patients, twenty-five presented themselves in person, and, on four others, recent cardiac clinic records were available. Of the former control patients, twenty-two came to see one of us, and the

Supra, see first footnote, page 1.



Graph II *A*.—The average weekly values of erythrocyte sedimentation rates and nonfilamented neutrophil counts for two consecutive winters.

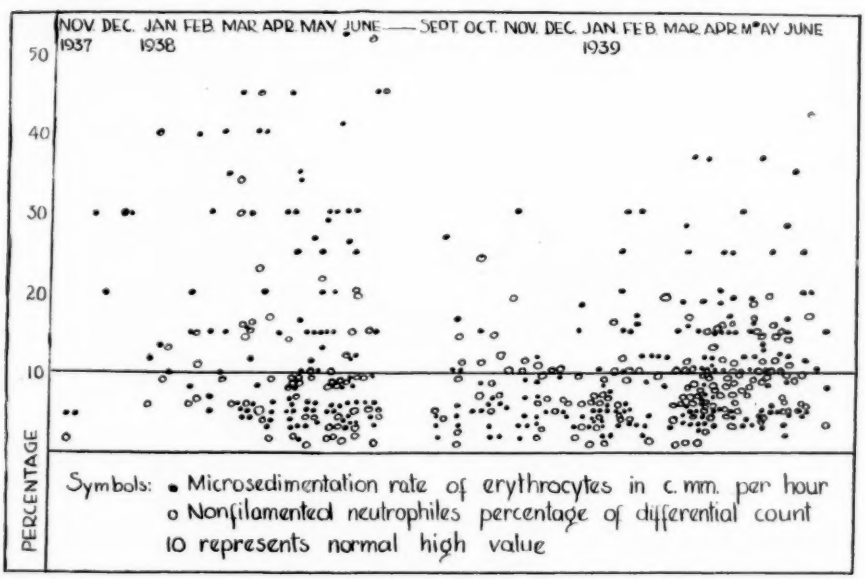


Graph II *B*.—Individual values of erythrocyte sedimentation rates and nonfilamented neutrophil counts in the treated patients from October, 1937, to June, 1939.

records of eight others contained enough recent clinical data to evaluate their state of health.

All of the treated and control patients who attended the follow-up clinic were re-examined and questioned in detail about their state of health for the preceding two years.

The average age of the previously treated patients in June, 1939 (at the time of re-examination), was 12 years, and among them there were fifteen males and fourteen females. The gain in weight for the two years was 20.6 pounds per child, and the number of colds, 1.8. Among the subacute rheumatic symptoms occurring more than twice in a given patient, there were abdominal symptoms in one, epistaxis in one, cardiac pain and dyspnea in two, headaches in one, and joint and muscle pains in two. Acute rheumatic fever recurred in two, or 7 per cent, of the patients.



Graph II *C*.—Individual values of erythrocyte sedimentation rates and nonfilamented neutrophil counts in control patients from November, 1937, to June, 1939.

The average age of the former control patients was 12.6 years. The gain in weight per child was 15.4 pounds, and the number of colds per child, three. Abdominal symptoms were prominent in six, cardiac pain and dyspnea in eight, epistaxis in two, headaches in seven, and joint and muscle pains in thirteen. There were ten attacks of rheumatic fever, an incidence of 33 per cent, with one death.

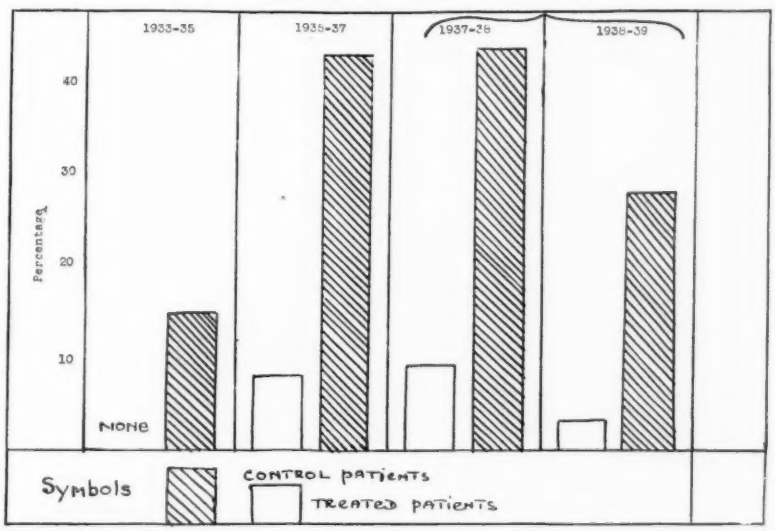
COMMENT

From the data presented here, it appears that inoculation with hemolytic streptococcus filtrate in patients known to have rheumatic fever continues, after six years, to have beneficial effects, i.e., it reduces the

number of rheumatic fever attacks, and, consequently, the incidence of carditis. Graph III summarizes the morbidity in the treated and control patients in the last six years.

Graph III shows the low relative incidence of acute rheumatic fever in the treated patients. So far as we know, the only factor extraneous to our treatment which may have contributed to the results is that the parents of perhaps half of the control patients declined to enlist their children in the treated group for the inadequate reason that they could not be bothered to send them to the clinic often enough—an indication of shiftlessness in these particular parents that manifested itself also in the general care of their children.

We realize that the total of sixty-six treated patients is too small a group from which to draw definitive conclusions. Nevertheless, the well-being of the treated patients throughout the past six years is impressive.



Graph III.—Diagrammatic presentation of comparative incidence of attacks of acute rheumatic fever in the treated and control patients between 1933 and 1939.

It is our intention to start the immunization of a new group of patients in the fall of 1939. For the past six months we have employed the pathogen selective test and the antistreptolysin titer estimation, in addition to our routine laboratory procedures,* to facilitate more precise estimation of rheumatic activity and its pathogenesis. Extensive studies on capillary resistance, blood platelets, and bleeding and coagulation time have been carried out in the last year, but since they do not cover the two-year period discussed in this article, they are not included in the results presented in this paper.

*Through the aid of a generous grant made by the John and Mary R. Markle Foundation.

THE PREDICTION OF DIFFERENCES BETWEEN PRECORDIAL LEADS CR, CL, AND CF, BASED ON LIMB LEAD FINDINGS

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OPINION is divided as to where to place the peripheral electrode in taking precordial electrocardiographic leads. There are advocates for the right arm (CR leads), the left arm (CL leads), and the left leg (CF leads), but evidence thus far available does not appear to justify a definite preference, in all cases, except from the standpoint of convenience.

The CR, CL, and CF leads differ from one another. In some patients they differ markedly. Fig. 1 illustrates this fact. In CR_4, T is inverted; in CL_4 it is upright; whereas, in CF_4, it is deeply inverted. When such marked variations are dependent on the position of the peripheral electrode, it would seem desirable to know, in advance, what they will be. In the following discussion we will show that this is possible. If the size and direction of a certain wave in any two of the three limb leads are known, its algebraic relations in the three precordial leads, CR, CL, and CF, can be predicted. To state the facts a little differently, if the size and direction of a certain wave in any two of the three limb leads are known, and if, in addition, its size and direction in one of the three precordial leads, CR, CL, or CF, are known, then its size and direction in the other two precordial leads can be predicted.

The fundamental principle which governs these predictions is not new. It is inherent in Einthoven's equation, namely, Lead I + Lead III = Lead II, as are the equations published by the Committee of the American Heart Association for the Standardization of Precordial Leads.[1] However, the practical application of this principle, for the purpose we mention, has not been emphasized.

A complete discussion of the relationships between the various precordial and limb leads could become extremely complex. It would have to consider the questions of the mode of production of action currents during activation of the cardiac muscle, the summation of these currents in the intricate aggregation of muscle bands which make up the heart, and their conduction to the body surface through tissues of various types. Fortunately, so far as our present purposes are concerned, these complex aspects of the question can be avoided. Discussion can begin with the electrical phenomena as they appear on the surface of the body. We are concerned with the differences of potential between various points on the skin, no matter how they are produced. We shall have to do with Einthoven's equation, Lead I + Lead III = Lead II, not with his controversial equilateral triangle hypothesis.

From the Edward B. Robinette Foundation, Medical Clinic, of the Hospital of the University of Pennsylvania.
Received for publication Nov. 13, 1939.

Before going further, it might be well to dispose of one point concerning terminology, and to review certain technical features of the electrocardiograph which have a bearing on what is to follow.

(a) In the ensuing discussion, for the sake of readily designating each of the two electrodes of a given lead, we shall give the name "terminal A" to the right arm connection in Leads I and II, and to the left arm connection in Lead III. We shall give the name "terminal B" to the left arm connection in Lead I and to the left leg connection in Leads II and III. In precordial leads, as they are now taken, the peripheral electrode is connected to "terminal A," and the precordial electrode to "terminal B."

(b) The electrocardiograph is so constructed that, if terminal A is connected to the negative pole of a battery and terminal B to its positive pole, an upward deflection of the string shadow will be produced. It follows, then, that an upright wave in any standard electrocardiographic lead signifies that terminal B is connected to a point of higher potential than terminal A during the inscription of that wave. Moreover, an inverted wave signifies just the reverse, i.e., that terminal A is connected to a point of higher potential than terminal B. When the string shadow is on the base line, terminals A and B are connected to points of equal potential.

(c) Just as the direction of a wave indicates which terminal (A or B) has the higher potential, so the amplitude of the wave indicates the potential difference between them. Thus, when the instrument is standardized in the usual way, a wave of plus 2 mm. in a given lead shows that, at the time of the peak of that wave, the potential of terminal B was 0.2 millivolt higher than that of terminal A.

METHOD OF PREDICTION

According to Einthoven's law, the algebraic sum of the deviations from the base line in Leads I and III, at any given instant, will equal the deviation in Lead II, i.e., Lead I + Lead III = Lead II, or, by transposing a term, Lead I = Lead II – Lead III. It follows, then, that if the size of any deflection in Lead I is known, the algebraic difference between that deflection in Leads II and III can be predicted.

(1) *Predicting the degree of difference.*—For example, if T_1 equals plus 2 mm., T_2 and T_3 must differ by 2 mm.

(2) *Predicting the direction of difference.*—An upright T_1 signifies that the right arm is a point of lower potential than the left arm during T-wave inscription. Therefore, if leads are taken from the right arm and from the left arm to a third point, such as the left leg, using the third point as terminal B in both, the lead using the point of lower potential (right arm) as terminal A, i.e., Lead II, will have a more positive T wave than the lead using the point of higher potential (left arm) as terminal A., i.e., Lead III. *Consequently, when T_1 equals plus 2, one can predict that T_2 will be 2 mm. more positive (or less negative) than T_3.*

It is easy to prove mathematically, and to show experimentally, that this relationship between Leads I, II, and III holds good not only when electrodes are on the arms and the left leg, but when they are on

any three areas of the body surface. Thus, if the three points used are the right arm, the left arm, and a point on the precordium, making the three leads I, CR, and CL, the mathematical relationships of Einthoven's equation hold equally well. In other words, just as it is possible to predict the algebraic difference between a wave in Lead II and one in Lead III when one knows its size and direction in Lead I, so is it possible to predict the algebraic difference between a wave in CR and one in CL when one knows its size and direction in Lead I. Applying the same principle, it is possible to predict, from Lead II, the algebraic difference between a wave in CR and CF; and it is possible to predict, from Lead III, the algebraic difference between a wave in CL and CF.

Fig. 1 serves as an example of the application of this principle; T_1 is minus 3, T_2 is plus 2, and T_3 is plus 5. At the peak of the T wave, Lead I shows that the potential of the right arm is 0.3 millivolt higher than that of the left arm; Lead II shows that the potential of the right arm is 0.2 millivolt lower than that of the left leg; and Lead III shows that the potential of the left arm is 0.5 millivolt lower than that of the left leg. Rearranging these facts makes it clear that, of the three, *the left arm has the lowest potential*—0.3 millivolt lower than the right arm, and 0.5 millivolt lower than the left leg. *The left leg has the highest potential*—0.2 millivolt higher than the right arm, and 0.5 millivolt higher than the left arm. The potential of the *right arm is intermediate* —0.3 millivolt higher than the left arm, and 0.2 millivolt lower than the left leg. Consequently, of the three precordial leads, CR, CL, and CF, *Lead CL, from the left arm (the point of lowest potential) to the precordium, will show the most positive T wave.* It will be 3 mm. more positive than the T wave in a lead from the right arm to the same point on the precordium (CR), and it will be 5 mm. more positive than the T wave in a lead from the left leg to the same point on the precordium (CF). Moreover, *Lead CF, from the left leg (the point of highest potential) to the precordium, will show the most negative T wave.* T in CF will be 2 mm. less positive than T in CR, and 5 mm. less positive than in CL. And, finally, *CR will show a T wave intermediate between the other two,* i.e., 3 mm. less positive than CL, and 2 mm. more positive than CF. Reference to Fig. 1 will show that these relationships hold good for all positions of the precordial electrode. In this example, both from position *2* and position *4*, the differences are great enough to make the wave upright in CL and inverted in CF.

By the use of this method, Table I has been constructed. At the left, it shows a number of possible configurations of T in limb leads. At the right, it shows the position of the peripheral electrode (right arm, left arm, or left leg) which will give the most positive, the intermediate, and the least positive T wave.

The accuracy of these predictions has been tested in seventy cases in order to be certain that the time element did not introduce too large an error. When T waves in limb leads are large, i.e., when, during T wave inscription, potential differences between extremities are large, the results are most clear cut. When T waves in limb leads are small, the application of the principle may be obscured by small differences in string standardization, or by the phasic variation in the size of the T wave so commonly seen in precordial leads. If these extraneous factors are not carefully excluded, they often obscure the accuracy of prediction of the quantitative differences between CR, CL, and CF, even when potential differences are large.

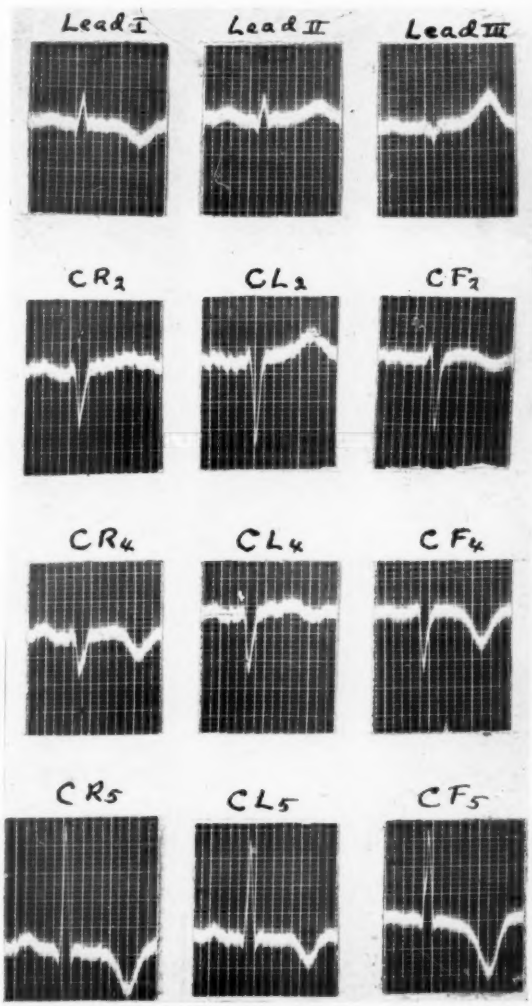

Fig. 1.—Electrocardiogram showing marked differences between the T waves in the three precordial leads, CR, CL, and CF, which are predictable from the size and direction of T in the limb leads (see Table I, Ex. 8). The details of the method of prediction are described in the text.

This method of prediction is applicable to other electrocardiographic deflections, as well as to the T wave.

The P Wave.—Table I may be used for P-wave prediction (see Fig. 2). In normals with an upright P wave in Leads I and II, CR will show the most positive P wave (see Table I, examples 1 to 4). In the average case of auricular flutter, the auricular wave has a pattern like example 7 in Table I. Consequently, CR and CL will show the most positive flutter wave.

TABLE I.

Examples	Limb Leads			When Paired with a Precordial Electrode:-*		
	T-1	T-2	T-3	The most normal (most + or least -) T wave will be obtained using the point of lowest potential, i.e.;	The intermediate T wave will be obtained by using the	The most abnormal (most - or least +) T wave will be obtained using the point of highest potential, i.e.,
(1)	2	4	2	R. arm 4	L. arm 2	L. leg 0
(2)	1	4	3	R. arm 4	L. arm 3	L. leg 0
(3)	4	4	0	R. arm 4		L. arm & L. leg 0
(4)	4	2	-2	R. arm 4	L. leg 2	L. arm 0
(5)	4	0	-4	R. arm & L. leg 4		L. arm 0
(6)	3	-1	-4	L. leg 4	R. arm 3	L. arm 0
(7)	0	4	4	R. arm & L. arm 4		L. leg 0
(8)	-3	1	4	L. arm 4	R. arm 1	L. leg 0
(9)	-4	0	4	L. arm 4		R. arm & L. leg 0
(10)	-4	-1	3	L. arm 4	L. leg 1	R. arm 0
(11)	-4	-4	0	L. arm & L. leg 4		R. arm 0
(12)	-1	-4	-3	L. leg 4	L. arm 1	R. arm 0
(13)	-2	-4	-2	L. leg 4	L. arm 2	R. arm 0

Table I.—In order to illustrate the prediction of quantitative, as well as qualitative, differences, arbitrary values have been given to the limb lead T waves, and an arbitrary value of zero has been assigned to the smallest precordial T wave (right hand column) in each example. The size of the T wave in the other two precordial leads has been calculated from these figures.

*Polarity as suggested by the Committee of the American Heart Association for the Standardization of Precordial Leads,[1] i.e., extremity electrode is electrode A; precordial electrode is electrode B.

The RS-T Segment.—Table I may also be used to predict the algebraic relations of RS-T segment deflections in CR, CL, and CF. This point will receive further discussion below.

The QRS Complex.—The same principle holds here as for the other deflections. However, during QRS inscription, movements of the string

are often very rapid. Consequently, in order to make the prediction it is necessary to have two leads recorded simultaneously in such a way as to bring out the time relations between them. Such predictions are therefore not practical for the average electrocardiographic laboratory.

The same relationship holds, if, instead of using the limbs and a precordial electrode, one applies the limb lead electrodes to any other three points on the body, and the "precordial" electrode to a fourth point. One of the experiments to illustrate this is shown in Fig. 3. The right arm electrode was applied just above the right nipple; the left arm electrode was applied just above the left nipple; and the left leg electrode was placed over the lower end of the sternum. With this set of connections, the tracing taken on Lead I (right nipple to left nipple) has a T wave of −8 mm.; the tracing taken on Lead II (right nipple to lower sternum) has a T wave of +2 mm.; and the tracing taken on Lead III (left nipple to lower sternum) has a T wave of +10 mm. Referring to the

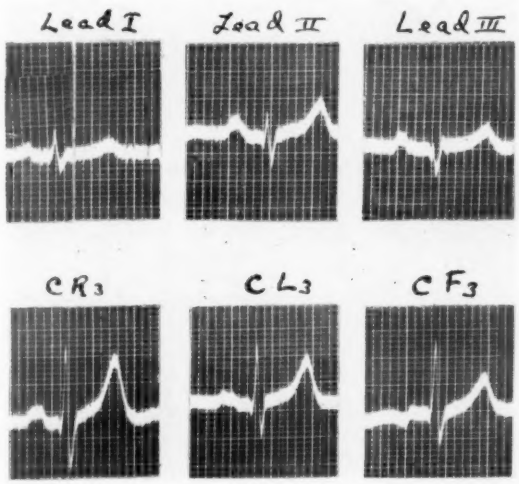

Fig. 2.—Electrocardiogram showing differences between the P waves in the three precordial leads, CR, CL, and CF, which are predictable from the size and direction of P in the limb leads. The P-wave pattern is that shown in Table I, Ex. 1.

appropriate example (i.e., No. 8) in Table I, it is clear that (1) the potential of the left nipple region is the lowest of the three; when it is paired with the fourth electrode (wherever that electrode may be placed on the body surface), it will give the most positive T wave (8 mm. more positive than the right nipple, and 10 mm. more positive than the lower sternum); (2) that the potential of the lower end of the sternum is the highest of the three, and, when paired with the fourth electrode, will give the least positive T wave (2 mm. less positive than the right nipple, and 10 mm. less positive than the left nipple; and (3) that the right nipple region has an intermediate potential, and, when paired with the fourth electrode, will give a T wave of intermediate size (8 mm. less positive than the left nipple, but 2 mm. more positive than the lower sternal

region). The experiment was done with the fourth electrode on a number of different places over the precordium and elsewhere. Fig. 3 shows the results when it was placed over the gall bladder region. Experiments were also done to study the effect of varying the position of the limb lead electrodes. Each time the predictions were verified by the tracings obtained.

These fundamental relationships might be stated in more general terms, as follows: If one chooses any three points (A, B, and C) on the body surface, and takes an electrocardiogram from A to B (Lead AB), from A to C (Lead AC), and from B to C (Lead BC), one can predict, from the size of T in any two of these three leads, which of the three points, when connected to a fourth point (P), will give the most positive T wave, which will give the most negative T wave, and which the intermediate T wave. If Lead AB shows a positive T wave, Lead AP will

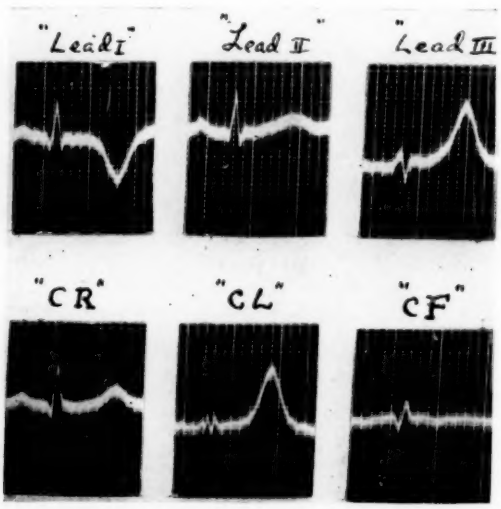

Fig. 3.—Electrocardiograms taken to show that the method of prediction described in this paper holds when the electrodes are placed on any four regions of the body surface.

The right arm electrode was placed just above the right nipple. The left arm electrode was placed just above the left nipple. The left leg electrode was placed over the lower end of the sternum. The "precordial electrode" was placed over the gall bladder.

Thus, "Lead I" is a lead from right nipple to left nipple, "Lead II" is from right nipple to lower sternum, "Lead III" is from left nipple to lower end of sternum, "CR" is from right nipple to gall bladder region, "CL" is from left nipple to gall bladder region, and "CF" is from lower end of sternum to gall bladder region. The T-wave pattern is that shown in Table I, Ex. 8.

have a more positive T wave than Lead BP. Moreover, the T wave in AP will be more positive than the T wave in BP by the amount of the size of the T wave in Lead AB. If Lead AB shows an isoelectric T wave, Leads AP and BP will have T waves of equal size. If Lead AB shows a negative T wave, Lead BP will have a more positive T wave than Lead AP. These predictions can be carried out for all possible locations of the four points. They can be verified by experiment, if one eliminates the errors to which electrocardiography is subject, i.e., differences in

string standardization, respiratory variations, and changes in position of the electrodes.

Finally, the question arises as to which of the three leads, CR, CL, or CF, is best. This cannot be answered at the present time, but the following facts may have a bearing upon the decision: (1) Patients with normal limb lead patterns (Table I, examples 1 to 4) will have the most positive T wave in CR, and the least positive T wave in CL or CF. (2) Patients with the usual limb lead pattern of acute pericarditis[2] will have the most marked elevation of the RS-T interval in CR, and the least marked elevation in CF. (3) In cases of recent posterior infarction, CF will show the most marked RS-T interval depression, and CL will

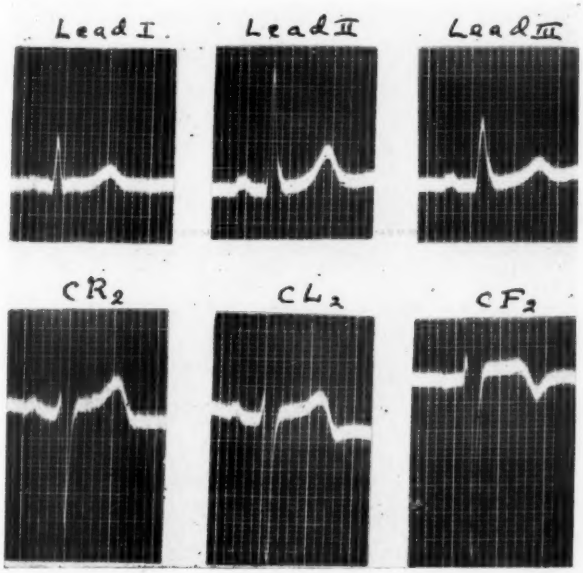

Fig. 4.—Electrocardiogram of a man, 55 years old, who had had an infarction of the anterior surface of the left ventricle four months before. At the present time the T waves are normal in the limb leads and in precordial leads CR and CL from positions 2, 3, 4, and 5. The only abnormality in T occurs in CF_3, in which there is a slight dip at the end of the wave, and in CF_2, in which there is a definite inversion. (The predictions in this tracing are shown in Table I, Ex. 1).

show the least. In cases of healed posterior infarction (Table I, examples 5 and 6), T-wave inversion will appear most frequently in CL, and least frequently in CF. (4) In cases of recent lateral infarction, CR would be most likely to show RS-T interval depression. (5) In cases of recent anterior infarction, in which the RS-T interval is elevated in Lead I, slightly depressed in Lead II, and definitely depressed in Lead III, CF will show a greater RS-T interval elevation than CR or CL. In cases of healed anterior infarction (Table I, examples 2, 7, and 8), CF will be more likely to show T-wave inversion than CR or CL.

Thus, it may be found that there is no "best lead." In one type of case, one of the extremities will be paired with the precordium, and, in

another type of case, another. At least, the choice of position for the peripheral electrode can be approached from a less empirical point of view than has been customary. One can decide whether the "most normal," or the "most abnormal" deflection is wanted, and place the peripheral electrode in such a way as to obtain whichever is desired.

One fact inclines us, at present, toward the use of CF as a routine lead. There is no question that the most important help obtained from precordial leads comes in the study of lesions of the anterior surface of the left ventricle. In this type of case, precordial leads often give the only electrocardiographic evidence of the patient's danger; the limb leads may be normal. In lesions located elsewhere in the heart, precordial leads might often be dispensed with, since the limb leads are likely to show diagnostic changes as well, or better. In cases of anterior infarction, in which we need help the most, CF leads are most likely to show an abnormality, both with recent and with healed lesions. In fact, cases of healing or healed anterior lesions are sometimes found in which the limb leads and the precordial leads CR and CL are normal, while the CF leads alone show T-wave inversion (see Fig. 4).

The entire question of the choice of position for the peripheral electrode must remain unsettled for the present. If CF leads are finally decided upon, for the reason just stated, there will be fewer "silent lesions." It is possible that there may be more "false positives," since normals would be most likely to show inverted T waves in CF leads. However, our studies of control groups suggest that when the precordial electrode is placed over the apex, an inverted T wave in the CF lead rarely occurs when the heart is normal.

CONCLUSIONS

1. If the size and direction of a certain electrocardiographic wave in two of the three limb leads are known, its algebraic relations in the precordial leads CR, CL, and CF can be predicted.

2. The method by which this can be done is described.

3. A table has been constructed in an attempt to simplify the process. It shows a number of limb lead patterns and the predicted differences between the T wave in the three precordial leads (CR, CL, and CF) for each pattern.

4. This table can be used to predict P-wave and RS-T interval relationships, also.

5. The principle underlying the prediction of these relationships is applicable not only when electrodes are placed on the two arms, the left leg, and the precordium, but when they are placed on any four points on the body surface.

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STUDIES ON THE TIME REQUIRED FOR THE ELIMINATION OF QUINIDINE FROM THE HEART AND OTHER ORGANS

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BECAUSE I found that quinidine was such a valuable drug in the treatment of heart disease, and because my experience with the drug had been so successful,[1, 2] I felt that further studies on it were warranted. A series of experiments was therefore undertaken to ascertain how much time is required for the elimination of quinidine from the blood, heart muscle, and other organs.

The length of time quinidine remains in the blood was recently reported.[3] The results, in brief, were as follows:

1. When a single dose, up to ten grains, of quinidine was given intravenously to dogs, less than 6 per cent of the drug was left in the blood stream by the end of seven minutes. This corroborates the work of Weiss and Hatcher.[4]

2. When a single dose of quinidine was given orally to patients, the maximum concentration in the blood was reached in about thirty minutes, and all of the quinidine had left the blood stream by the end of one hour.

3. When repeated, small doses of quinidine were given to patients orally, the maximum concentration in the blood was reached in about one hour. All of the quinidine had left the blood stream by the end of one and one-half hours after the last dose was given.

It is the purpose of this paper to report the time required for the elimination of quinidine from the heart, lungs, liver, and other organs, after giving the drug in various amounts orally to dogs, and to present the method used in determining the amount of quinidine in the tissues and blood.

METHOD FOR THE QUANTITATIVE DETERMINATION OF QUINIDINE SULFATE IN TISSUES AND BLOOD

I. *Tissues.*—Five grams of well-ground tissue are placed in a beaker. Add sufficient distilled water (usually about 100 c.c.) to cover the material. Boil over a steam bath for about two hours, until a flocculent precipitate is formed. Add 3 c.c. of 40 per cent NaOH. Boil again over a steam bath until the volume is reduced to about 50 c.c. Place in a separatory funnel and add warm water washings from the beaker. Allow the solution to cool. Extract with ether three times,

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using about 50 c.c. each time. Shake each extraction for fifteen to twenty minutes. Evaporate the ether and dissolve the extract in water (distilled) slightly acidified with dilute H_2SO_4. Warm over the steam bath and place in the same funnel in which the ether extraction was done. Make the solution alkaline with NaOH. Extract again, three times, using 50 c.c. of chloroform each time. Shake each extraction fifteen to twenty minutes. Evaporate the chloroform from the three extractions.

Dissolve the residue in 5 c.c. of slightly acidulated water.

Take 1 c.c. of this acidulated water solution and place in a small, glass-stoppered container.

Add 2 c.c. of 0.02 normal potassium bromate solution, 0.20 Gm. of potassium bromide, and 0.25 c.c. of 4 normal HCl.

Allow to stand for ten minutes (for complete reaction between quinidine and bromine), and then add 0.3 Gm. of potassium iodide crystals.

Allow solution to stand ten minutes.

Titrate against 0.02 normal solution of sodium thiosulfate, using starch solution as an indicator.

Equation involved.—

$$KBrO_3 + 5\ KBr + 6\ HCl = 6\ KCl + 3\ H_2O + 3\ Br_2$$

$$Br_2 + 2KI = 2\ KBr + I_2$$

The addition of the 4 normal HCl to the solution containing the quinidine, potassium bromate, and potassium bromide causes a reaction between the latter two compounds which results in the liberation of free bromine. The amount of free bromine liberated is exactly equivalent to the amount of potassium bromate that was added to the solution. After the reaction between the free bromine and the quinidine is complete, the addition of 0.3 Gm. of potassium iodide takes up the excessive amount of free bromine, forming potassium bromide and liberating free iodine. The amount of free iodine present is determined by titrating against the sodium thiosulfate solution. This amount of free iodine is exactly equivalent to the amount of free bromine left over after the reaction of the bromine and the quinidine. Since the amount of free bromine liberated from a given amount of potassium bromate and the amount of free bromine remaining after its combination with the quinidine are known, it is possible, by calculating the difference between these two quantities, to determine the amount of bromine that reacted with the quinidine.

The detection of such small quantities of quinidine sulfate was made possible by the construction by Dr. A. D. Hirschfelder of a special microburette from a Kahn pipette. Amounts as small as 0.005 mg. of quinidine sulfate can be detected by this method.

It is very important that only 3 c.c. of 40 per cent NaOH solution be added to a 5-gram tissue solution, and from 15 to 18 c.c. of 40 per cent NaOH to twenty-five grams of tissue sample. There is danger of the formation of a strong emulsion, with almost a solidification of fat, from which the ether does not separate readily even after allowing the emulsion to stand for several days.

The amounts of 0.02 normal $KBrO_3$ solution, 4 normal HCl, and KBr and KI which are used in the general procedure are sufficient to detect from 0.005 to 0.2 mg. per c.c. of quinidine sulfate. For higher concentrations of quinidine sulfate these amounts should be increased accordingly.

Six milligrams of quinidine sulfate per c.c. can be estimated by this method; beyond this, the formation of a heavy precipitate after the KI is added to the solution interferes with the titration. Therefore, it is recommended that the samples be diluted to a proper concentration. If larger amounts of 4 normal HCl are used, lower yields are obtained.

II. *Blood.*—Five cubic centimeters of whole, oxalated blood are taken with a blood pipette and allowed to spread over 20 c.c. of chloroform in a separatory funnel. Twelve to sixteen drops of 30 per cent NaOH are allowed to drop over the blood surface gradually. The blood begins to char, and, upon careful shaking, it crumbles and turns into a powderlike substance. The blood is then extracted three times, using 20 c.c. of chloroform each time, after which the procedure is the same as for tissues.

Titration of Water Blanks

	Quinidine equivalent in mg./c.c.
Sample 1	+0.001
Sample 2	-0.002
Sample 3	0.000
Sample 4	+0.001

Titration of Chloroform Blanks

	Quinidine equivalent in mg./c.c.
Sample 1	+0.002
Sample 2	-0.001
Sample 3	-0.001
Sample 4	0.000

*Determination of "Unknown" Amounts of Quinidine Sulfate in Water Solution**

SAMPLE	AMOUNT PER C.C.	AMOUNT FOUND	PER CENT ERROR
1	0.02 mg.	0.0195	- 2.5
2	0.05 mg.	0.058	+16.0
3	0.08 mg.	0.076	- 5.0
4	0.01 mg.	0.0099	negligible
5	0.5 mg.	0.520	+ 4.0
6	0.005 mg.	0.0054	+ 8.0
7	0.2 mg.	0.183	- 8.5

Titration of Blanks on Blood (Human)

	Quinidine equivalent in mg./c.c.
Sample 1	+0.003
Sample 2	+0.001
Sample 3	-0.006
Sample 4	-0.001
Sample 5	+0.002

Titration of "Unknown" Amounts of Quinidine in Blood (Human)

SAMPLE	TRUE AMOUNT (MG./C.C.)	AMOUNT FOUND	PER CENT ERROR
1	0.50	0.508	+1.6
2	0.50	0.5007	negligible
3	0.50	0.489	-2.2
4	0.30	0.3024	+0.8
5	0.30	0.2934	-2.1
6	0.2018	0.2016	negligible
7	0.10	0.098	-2.0
8	0.932	0.890	-4.5

Titration of Tissue Blanks

(5 Gm. beef heart used)

	Quinidine equivalent in mg./Gm.
Sample 1	+0.001
Sample 2	+0.002
Sample 3	-0.001

*All unknowns were prepared by Dr. A. D. Hirschfelder.

TABLE I

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE AND OTHER ORGANS AFTER GIVING SMALL, SINGLE DOSES, ORALLY (DOGS)

DOG NO.	SEX	WT. IN KILOS	ORAL DOSE IN MG.	TIME AFTER LAST DOSE	WT. OF HEART	MG. OF "Q" PER GM. WT.	MG. IN TOTAL HEART	% "Q" IN HEART	WT. OF LUNG	MG. OF "Q" PER GM. WT.	WT. OF LIVER	MG. OF "Q" PER GM. WT.	WT. OF KIDNEY	MG. OF "Q" PER GM WT.	WT. OF SPLEEN	MG. OF "Q" PER GM. WT.
1	F	21.3	100	30 min.	171.1	0.046	7.87	7.87								
2	M	19.90	100	1 hour	186.0	0.035	6.51	6.51								
3	M	18.60	100	2 hours	174.0	0.023	4.00	4.00								
4	F	19.30	100	3 hours	143.5	0.017	2.44	2.44	243.5	0.00	645.5	0.00	107.0	0.00	51.5	0.00
5	M	20.4	100	4 hours	160.5	0.000	0.00									

Titration of "Unknown" Amounts of Quinidine in Tissue

(5 Gm. beef heart)

SAMPLE	TRUE AMOUNT (MG./GM.)	AMOUNT FOUND	PER CENT ERROR
1	0.60	0.567	-5.5
2	0.50	0.518	+3.6
3	0.60	0.592	-1.3
4	0.50	0.452	-9.6
5	0.20	0.204	+2.0

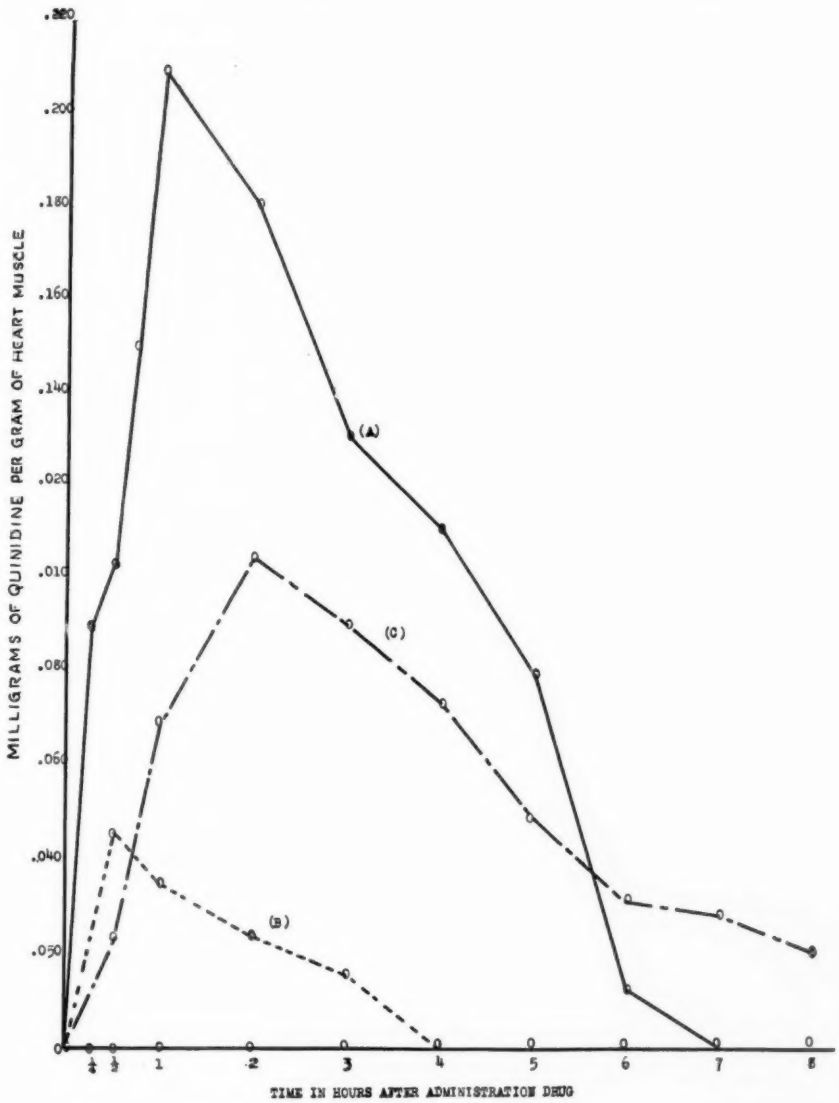

Fig. 1.—Length of time quinidine remains in the heart muscle. (*A*), After giving single, large dose—585 mg. (*B*), After giving single, small dose—100 mg. (*C*), After giving three 200-mg. doses—one hour apart (orally, to dogs).

TABLE II

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE AND OTHER ORGANS AFTER GIVING SINGLE, LARGE DOSES, ORALLY (DOGS)

DOG NO.	SEX	WT. IN KILOS	ORAL DOSE IN MG.	TIME AFTER LAST DOSE	WT. OF HEART	MG. OF "Q" PER GM. WT.	MG. IN TOTAL HEART	% "Q" IN HEART	WT. OF LUNG	MG. OF "Q" PER GM. WT.	MG. IN TOTAL LUNG	WT. OF LIVER	MG. OF "Q" PER GM. WT.	MG. IN TOTAL LIVER	WT. OF KIDNEY	MG. OF "Q" PER GM. WT.	MG. IN TOTAL KIDNEY	WT. OF SPLEEN	MG. OF "Q" PER GM. WT.	MG. IN TOTAL SPLEEN	TOTAL % RECOVERED
1	M	20.9	585	15 min.	166.2	0.090	14.9	2.7													
2	M	20.9	585	30 min.	127.5	0.105	13.4	2.5													
3	M	16.3	585	45 min.	128.9	0.150	19.3	3.5													
4	F	15.0	585	1 hour	110.0	0.209	22.9	4.2													
5	M	21.8	585	2 hours	143.4	0.181	25.9	4.8	186.5	0.305	56.88	495.0	0.608	300.9	(1 kidney) 42.4	0.328	13.9	79.2	0.170	13.46	76.1
6	M	20.9	585	3 hours	179.3	0.131	23.4	4.3	164.5	0.140	23.03	556.5	0.445	247.6	115.7	0.052	6.0	60.5	0.088	5.32	56.5
7	M	22.3	585	4 hours	173.5	0.111	19.2	3.5	180.7	0.119	21.50	451.8	0.111	50.14	91.0	0.170	15.47	93.4	0.088	8.22	21.2
8	M	22.7	585	5 hours	162.5	0.080	13.0	2.4	193.6	0.072	13.94	488.2	0.070	34.17	84.4	0.013	1.09	92.8	0.070	6.49	12.7
9	M	20.4	585	6 hours	153.2	0.013	2.0	0.37	152.4	0.082	12.50	567.5	0.013	7.37	93.7	0.131	12.27	60.3	0.072	4.34	7.1
10	M	20.0	585	7 hours	141.1	0.000	0.0	0.00	157.1	0.056	8.80	706.1		-----	93.5	0.095	8.88	91.5	0.076	6.95	4.5

Length of time quinidine remains in the heart muscle after giving a single small dose (100 milligrams).—When a single small dose of quinidine was given orally to dogs, the maximum concentration of the drug in the heart muscle was reached in about thirty minutes. No quinidine was found in the heart muscle at the end of four hours (Table I, Fig. 1).

Length of time quinidine remains in the heart muscle after giving a single large dose (585 milligrams).—When a single large dose of quinidine was given orally to dogs, the maximum concentration of the drug in the heart muscle was reached in about one hour. It was seven hours before the quinidine had disappeared entirely from the heart muscle (Table II, Fig. 1).

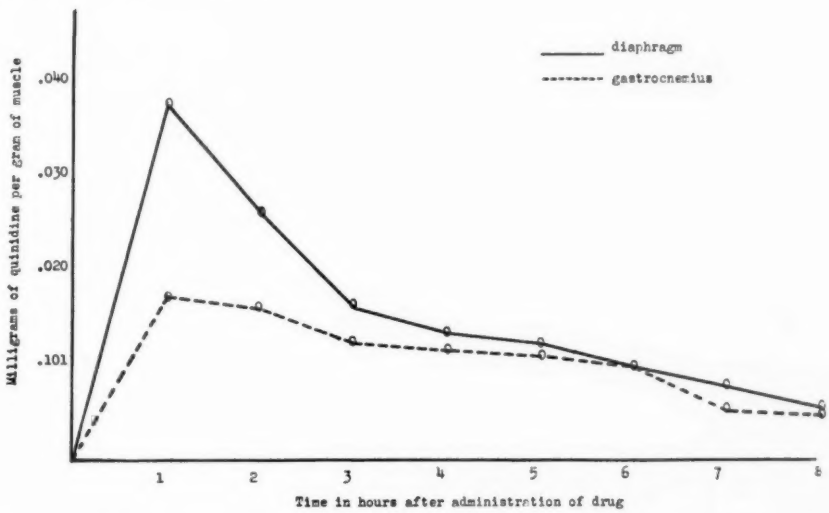

Fig. 2.—Length of time quinidine remains in diaphragm and gastrocnemius muscle after giving three 200-mg. doses, orally, one hour apart (dogs).

Length of time quinidine remains in the heart muscle after giving repeated, small doses.—When small doses (100 mg.) of quinidine were given at one-hour intervals, the maximum concentration of the drug in the heart muscle was reached in one hour when two doses were given (Table III). When three and four doses, respectively, were given at one-hour intervals, the maximum concentration of the drug in the heart was reached in two hours (Tables IV and V).

It was about six hours before the drug disappeared entirely from the heart muscle.

Length of time quinidine remains in the heart muscle after giving a single dose of 585 mg. and three 200-mg. doses one hour apart (dogs, orally).—The purpose of this experiment was to compare the length of time quinidine remains in the heart muscle when one, single, large dose is given, and when a similar amount is given, but is divided into three

TABLE III

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE AND OTHER ORGANS AFTER GIVING TWO 100-MG. DOSES ONE HOUR APART (DOGS)

DOG NO.	SEX	WT. IN KILOS	DOSE IN MG.	TIME AFTER LAST DOSE	WT. OF HEART	MG. OF "Q" PER GM. WT.	WT. OF LIVER	MG. OF "Q" PER GM. WT.	WT. OF LUNGS	MG. OF "Q" PER GM. WT.	WT. OF KIDNEY	MG. OF "Q" PER GM. WT.	WT. OF SPLEEN	MG. OF "Q" PER GM. WT.
1	M	19.1	2-100 mg.	½ hour	166.0	0.08	611.7	0.072	187.2	0.066	154.5	0.079	54.5	0.043
2	F	25.9	2-100 mg.	1 hour	266.0	0.101	845.5	0.055	281.0	0.065	178.4	0.092	54.7	0.068
3	M	20.9	2-100 mg.	2 hours	212.5	0.078	813.5	0.025	207.8	0.02	160.0	0.055	80.7	0.06
4	M	18.6	2-100 mg.	3 hours	177.5	0.04	554.0	0.013	218.0	0.015	121.2	0.023	118.7	0.017
5	M	18.0	2-100 mg.	4 hours	153.5	0.015	316.0	Traces	151.8	0.011	108.8	0.014	78.4	Traces

TABLE IV

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE AND OTHER ORGANS AFTER GIVING THREE 100-MG. DOSES ONE HOUR APART (DOGS)

DOG NO.	SEX	WT. IN KILOS	DOSE IN MG.	TIME AFTER LAST DOSE	WT. OF HEART	MG. OF "Q" PER GM. WT.	WT. OF LIVER	MG. OF "Q" PER GM. WT.	WT. OF LUNGS	MG. OF "Q" PER GM. WT.	WT. OF KIDNEY	MG. OF "Q" PER GM. WT.	WT. OF SPLEEN	MG. OF "Q" PER GM. WT.
1	M	20.4	3-100 mg.	½ hour	172.6	0.089	648.5	0.066	171.5	0.107			95.8	0.037
2	M	20.4	3-100 mg.	1 hour	200.7	0.068	507.0	0.064	192.9	0.070			123.5	0.123
3	M	19.7	3-100 mg.	2 hours	117.7	0.133	442.3	0.078	195.7	0.244			87.5	0.088
4	M	19.5	3-100 mg.	3 hours	171.0	0.093	405.0	0.088	145.5	0.058			143.7	0.085
5	M	21.6	3-100 mg.	4 hours	130.4	0.049	569.5	0.088	135.7	0.043			96.7	0.080
6	M	19.3	3-100 mg.	5 hours	154.1	0.005	476.0	0.084	188.7	0.025			94.3	0.064

TABLE V

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE AND OTHER ORGANS AFTER GIVING FOUR 100-MG. DOSES ONE HOUR APART (DOGS)

DOG NO.	SEX	WT. IN KILOS	DOSE IN MG.	TIME AFTER LAST DOSE	WT. OF HEART	MG. OF "Q" PER GM. WT.	WT. OF LIVER	MG. OF "Q" PER GM. WT.	WT. OF LUNGS	MG. OF "Q" PER GM. WT.	WT. OF KIDNEY	MG. OF "Q" PER GM. WT.	WT. OF SPLEEN	MG. OF "Q" PER GM. WT.
1	M	18.8	4-100	½ hour	165.9	0.076	470.0	0.039	202.5	0.049	97.6	0.047	119.4	0.074
2	M	19.3	4-100	1 hour	171.0	0.056	589.0	0.058	200.0	0.062	94.0	0.092	106.0	0.080
3	M	21.0	4-100	2 hours	192.5	0.088	585.0	0.082	195.0	0.099	107.5	0.142	137.0	0.088
4	F	18.2	4-100	3 hours	134.0	0.052	520.0	0.043	139.5	0.068	64.5	0.092	50.0	0.033
5	M	21.9	4-100	4 hours	190.0	0.021	717.0	0.019	173.7	0.035	92.7	0.041	229.8	0.015
6	F	25.0	4-100	5 hours	152.6	0.016	520.0	0.010	158.0	0.025	111.5	0.029	93.3	0.009

equal doses, one hour apart. When a large, single dose of quinidine is given, the height of concentration of the drug in the heart is reached in about one hour, and it is about seven hours before all of the quinidine is eliminated. When three 200-mg. doses of quinidine are given one hour apart, it takes about two hours for the drug to reach its maximum concentration in the heart muscle, and it is about nine hours before it is all eliminated (Table VI, Fig. 1). The maximum concentration of

TABLE VI

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE, DIAPHRAGM, AND GASTROCNEMIUS MUSCLE AFTER GIVING THREE 200-MG. DOSES ONE HOUR APART, ORALLY, TO DOGS

DOG NO.	SEX	WT. IN KILOS	TIME KILLED	WT. OF HEART	MG./ GM. WT.	WT. OF DIAPHRAGM	MG./ GM. WT.	WT. OF GASTROCNEMIUS	MG./ GM. WT.
1	M	19.7	½ hr.	162.1	0.0234		0.013		
2	M	20.4	1 hr.	195.2	0.069	97.5	0.039	92.5	0.018
3	M	18.6	2 hr.	166.2	0.105	115.2	0.026	69.5	0.016
4	M	25.0	3 hr.	257.8	0.091	147.8	0.016	93.8	0.013
5	M	19.5	4 hr.	170.0	0.074	140.6	0.0139	76.6	0.0118
6	M	16.3	5 hr.	138.0	0.049	86.7	0.0130	59.3	0.0107
7	M	19.0	6 hr.	178.7	0.032	96.4	0.010	83.5	0.01
8	M	23.5	7 hr.	172.5	0.291	97.3	0.0093	81.4	0.0062
9	M	20.0	8 hr.	127.0	0.0217	108.3	0.0061	104.6	0.0052

quinidine in the heart was about 0.209 mg. per gram of heart muscle when the single large dose was given, whereas it was only 0.105 mg. per gram of heart muscle when a slightly greater amount was given in divided doses at hourly intervals. Weiss and Hatcher,[4] Korns,[5] and Gordon, Matton, and Levine[6] have shown that a much greater amount of quinidine could be tolerated when it was divided over a period of time than when it was given in a single large dose. Lewis, Drury, Wedd, and Iliescu[7] showed that the degree of slowing of the auricular rate depended on the dose of quinidine.

Length of time quinidine remains in the lung, liver, kidney, and spleen.—Few studies were made on these organs after single, small doses were given, but it will be noticed (Table I) that at the end of four hours no quinidine was found in any of them. At the end of the fifth hour no quinidine was found in the heart muscle. It appears, then, that quinidine leaves the lungs, liver, kidneys, and spleen at about the same rate as it leaves the heart muscle, when single, small doses are given.

When a single, large dose of quinidine is given, again it appears that the maximum amount of the drug reaches these organs before the two-hour period (Table II). It may be that higher concentrations of quinidine are reached in these organs before the two-hour period. The largest amount of quinidine was taken up by the liver. The drug remained in all of the other organs longer than it did in the heart, with the exception of the liver. No quinidine was found in the liver or the heart at the end of seven hours.

Length of time quinidine remains in the heart, diaphragm, gastrocnemius and heart muscle after giving three 200-mg. doses one hour apart (dogs, orally).—The purpose of this experiment was to see whether activity of a muscle was the determining factor in the amount of quinidine taken up by that muscle. It was found that, after giving a dog three 200-mg. doses of quinidine one hour apart (Table VI), the heart took up the greatest amount of the drug; the diaphragm was next, and the gastrocnemius took up the least amount. At the end of one hour after taking the quinidine, there were 0.069 mg. of quinidine per gram of muscle in the heart, 0.039 mg. of quinidine per gram of muscle in the diaphragm, and 0.018 mg. of quinidine per gram of muscle in the gastrocnemius muscle (Table VI, Figs. 1 and 2). At the end of two hours, there were 0.105 mg. of quinidine per gram of muscle in the heart, 0.026 mg. per gram of muscle in the diaphragm, and 0.016 mg. per gram of muscle in the gastrocnemius muscle. It appears from these experiments that the more active muscles take up the greatest amount of quinidine.

Length of time quinidine remains in the skeletal muscles.—A dog weighing 9 kg. was given 585 mg. of quinidine by mouth. Three kilograms of skeletal muscle were removed from this dog one hour after the drug had been administered. The amount of quinidine per gram of muscle was found to be 0.011 mg.

Length of time quinidine remains in the liver, lungs, kidneys, and spleen after giving small doses at one-hour intervals.—After giving the dog two 100-mg. doses of quinidine one hour apart, the maximum concentration of the drug is reached in all these organs in about one hour. When three and four doses are given, it is about two hours before the concentration reaches its maximum in these organs. The drug is gradually eliminated by these organs, so that at the end of five hours very little is found (Tables IV and V). It will be noticed that the rate of absorption and elimination from the lungs, liver, kidneys, and spleen is very similar to that of the heart muscle.

SUMMARY AND CONCLUSIONS

1. After quinidine had been given orally to dogs, the rate of its absorption and elimination by the heart muscle, liver, lungs, kidneys, spleen, diaphragm, and gastrocnemius and other skeletal muscles was studied.

2. When single doses of 100 mg. were given, the maximum concentration of quinidine in the heart muscle was reached in about thirty minutes. No trace of the drug was found in the heart muscle at the end of four hours.

3. When a single, large dose of 585 mg. of quinidine was given, the maximum concentration was reached in about one hour. It was seven hours before no trace of quinidine was to be found in the heart muscle.

The lungs, liver, kidney, and spleen took up the drug at a rate similar to that of the heart, so that at the end of seven hours very little of the drug remained in any of these organs.

4. When repeated, small doses of quinidine were given at one-hour intervals, the maximum concentration of the drug in the heart was reached in about one hour when only two doses were given, and in about two hours when three and four doses were given one hour apart. Very little quinidine remained in the heart at the end of five hours. The lungs, liver, kidney, and spleen took up the drug at a similar rate, but the rate of elimination from these organs was perhaps a little slower than it was from the heart.

5. When a large, single dose of quinidine is given, the maximum concentration of the drug in the heart muscle is reached in about one hour. It is about seven hours before all of the drug leaves the heart. When the same amount of quinidine is given in three divided doses, at one-hour intervals, the maximum concentration of the drug in the heart muscle is reached in about two hours, and attains a value of not more than 50 per cent of that produced by giving a single dose. It is more than eight hours before all of the quinidine leaves the heart muscle.

6. It appears that the more active muscles absorb the most quinidine. When three 200-mg. doses of quinidine are given at one-hour intervals, at the end of one hour the heart has absorbed twice as much as the diaphragm, and the diaphragm twice as much as the gastrocnemius muscle.

7. A method is presented for the extraction and quantitative determination of the quinidine content of the blood and tissues.

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RESPONSES OF THE NORMAL HEART AND THE HEART IN EXPERIMENTAL VITAMIN B_1 DEFICIENCY TO METABOLITES (PYRUVIC ACID, LACTIC ACID, METHYL GLYOXAL, GLYCERALDEHYDE, AND ADENYLIC ACID) AND TO THIAMIN*

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PREVIOUS study on rats[1] has demonstrated changes in the heart rate and electrocardiographic complexes, as well as in the responses to drugs, in vitamin B_1 deficiency. This work has now been extended in order to seek the cause of these abnormalities in deficient animals. Disturbances of the intermediary carbohydrate metabolism of the cells of the body are believed to occur in this deficiency, since the lack of vitamin B_1 prevents the normal disposal of pyruvic acid and, indirectly, of lactic acid. In vitamin B_1 deficiency these and other metabolites accumulate in the body.[2, 3, 4, 5, 6, 7] The question, therefore, has been raised whether the symptoms and physiologic changes in vitamin B_1 deficiency are caused by a failure of tissue metabolism, per se, or by the accumulation of toxic products resulting therefrom. The effects of the latter have been investigated. By the administration of various metabolites we have attempted either to produce in normal rats electrocardiographic or other changes characteristic of vitamin B_1 deficiency, or to precipitate in partially deficient rats a severely deficient state. It was also considered desirable to obtain information on the pharmacology of these metabolites.

METHOD OF INVESTIGATION

The preparation of a diet deficient in vitamin B_1 and the method of taking electrocardiograms have been described previously.[1] In this investigation, the yeast in the deficient diet was treated with 0.1 N sodium hydroxide and autoclaved (15 pounds pressure) for six hours at a pH of 7 to 8. In part of the work, washed casein† was used without rewashing. Rats were kept for long periods on the deficient diet; each time that the decrease in heart rate and weight indicated that the rats were moderately deficient, they were given subcutaneous injections of synthetic crystalline vitamin B_1‡ (thiamin hydrochloride). Fresh dilutions of 1 to 50 or 1 to 100 were made up daily from 0.1 per cent stock solu-

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†Obtained from A. H. Thomas Company.

‡Usually Betaxin (Winthrop) was used; in a few cases it was Betabion (Merck). Both were generously supplied for this work.

tions. Doses of 0.016 mg. regularly brought about a rapid increase in heart rate and weight. The number of days between such doses is only a rough estimate of the maintenance period for this amount of thiamin because of the difficulty of bringing rats to the same state of deficiency before each dose. Control rats were fed either a control diet, similar to the deficient diet but containing unautoclaved yeast, or a diet of bread and milk supplemented by cod-liver oil, iron ammonium citrate, and yeast.

Standardized electrocardiograms were recorded on paper, which was run at a speed of 100 mm. per second in order to allow analysis of the complexes. In records of normal rats the T waves have usually been found to be upright or flat in Lead I, and upright in Leads II and III. In rats, T_1 is usually very low. Only changes of more than thirty beats per minute in the heart rate, or 1 mm. in the height of the T waves, have been accepted as being outside normal limits. A few experiments, in which irregular variations of more than thirty beats appeared, have been designated as showing no change in heart rate. Only marked changes in the height of the origin of the T waves have been noted, since considerable variation caused by movement or other factors has been observed in control records on normal rats.

In order to determine the sensitivity and cardiac response of normal rats and of rats deficient in vitamin B_1 to various metabolites, three types of experiments were performed on each group of animals: (1) The fatal doses of the substances under investigation were determined approximately, using various routes of administration. In some cases, however, the amount of chemical material and the number of deficient rats available did not permit extensive trials. (2) Short experiments were carried out in which electrocardiograms were recorded before, and at frequent intervals for several hours after, the administration of smaller doses of the metabolites. Rats kept on a diet deficient in vitamin B_1 were usually used when they were not in a severely deficient state, that is, when the heart rate had fallen to 300 to 400 beats per minute and before neurologic symptoms had disappeared.

(3) Longer experiments were performed, in which 1 to 3 doses of the metabolite studied were administered daily over a period of several weeks. At intervals of several days, or oftener, if necessary, electrocardiograms were recorded before, and for a few hours after, the daily doses. In a number of experiments the body weight and food intake were also measured. In deficient rats the heart rate or body weight, or both, have been used as criteria for judging the speed with which rats became deficient and the severity of the deficiency.

Doses of the substances administered were always expressed in terms of milligrams per 100 grams of body weight. Pyruvic,* lactic,† and adenylic‡ acids were neutralized with sodium hydroxide to pH 7, and diluted to contain a desired percentage of acid by weight. The strength of the solutions used depended on the amount to be given and on the route of administration. When administered orally the solutions were given by means of a small woven catheter, used as a stomach tube. A small series of intravenous injections were made into the exposed femoral vein, with or without ether anesthesia.

Pyruvic and lactic acids were studied somewhat more extensively than other metabolites, because of evidence in the literature relating them to vitamin B_1 deficiency. Experiments on methyl glyoxal, glyceraldehyde, and adenylic acid were also carried out, as well as certain control experiments, using sodium bicarbonate, ammonium chloride, and glucose. Additional observations on the cardiac effect of

*Obtained from Eastman Kodak Company.

†Baker's Analyzed.

‡Prepared and purified by Dr. F. P. Nabenhauer, of the Smith, Kline, and French Laboratories.

large doses of vitamin B_1, as well as of the lack of certain vitamins other than B_1, were also made.

RESULTS

Pyruvic Acid ($CH_3.CO.COOH$)

Vitamin B_1 has been regarded as a catalyst which brings about the oxidation of pyruvate in brain tissues.[8] Pyruvic acid has been found in increased amounts in the blood of rats and of pigeons deficient in vitamin B_1,[2, 9] as well as in patients with "wet" beriberi.[3, 7] Lu[10] has shown that the blood pyruvate values in rats rose progressively as the heart rate fell. It has not been definitely proved, however, that the presence of pyruvic acid is responsible for the symptoms of polyneuritis.[11] The effects of injecting pyruvate into animals and man have been discussed by Wilkins, Weiss, and Taylor,[12] who administered sodium pyruvate orally and intravenously to normal subjects and to patients with beriberi. In the latter group they found that the sodium pyruvate tolerance curve was occasionally increased in height, but a definite deviation from the normal was not observed. In normal and deficient persons, electrocardiograms after giving sodium pyruvate showed lengthening of the Q-T interval and a minor, but definite, decrease in the amplitude of the T waves. These temporary changes were probably caused, at least in part, by alkalosis. Kalaja and Närvanen[13] found that the subcutaneous injection of pyruvic acid decreased the heart rate of rats, but not of pigeons and rabbits, and that this effect was somewhat greater than that produced by lactic acid. Lu[10] observed no change in the heart rate of rats and rabbits after the intravenous injection of pyruvate in doses producing blood pyruvate levels which were above the highest occurring in vitamin B_1 deficiency.

Sodium Pyruvate, Administered Orally.—Two normal rats developed marked diarrhea, but recovered, after doses as high as 713 and 800 mg. per 100 grams of body weight. The fatal dose for deficient rats was approximately 600 mg. (Table I). In normal and deficient rats which received smaller single doses of pyruvate the heart rate remained unchanged, but in two out of four deficient rats the T waves were higher, or had a higher origin, after pyruvate (Table II).

TABLE I

FATAL DOSES OF CHEMICAL SUBSTANCES FOR NORMAL AND DEFICIENT RATS

	ORALLY		SUBCUTANEOUSLY	
	NORMAL RATS	DEFICIENT RATS	NORMAL RATS	DEFICIENT RATS
	(MG. PER 100 GRAMS BODY WT.)		(MG. PER 100 GRAMS BODY WT.)	
Sodium Pyruvate*	Over 800	600	275-300	150-175
Pyruvic Acid	300	350	--	--
Sodium Lactate*	500-700	Over 700	350-400	Over 450
Lactic Acid	550	Over 500	--	--
Methyl Glyoxal	175-200	Over 200	--	--
Glyceraldehyde	Over 600	Over 600	--	--

*Expressed as mg. of acid per 100 grams of body weight.

TABLE II

ELECTROCARDIOGRAPHIC CHANGES IN RATS AFTER SINGLE DOSES OF SODIUM PYRUVATE AND PYRUVIC ACID

	NUTRITIONAL STATE	NO. OF RATS	DOSAGE* (MG. PER 100 GRAMS BODY WT.)	EFFECT ON HEART RATE			NUMBER OF RATS AND EFFECT ON T WAVES			REMARKS
				INCREASE	NO CHANGE	DECREASE	INITIAL FORM OF T WAVES	NO CHANGE	FORM OF T WAVES AFTER ADMINISTRATION OF SUBSTANCE	
Sodium Pyruvate p.o.	Normal	4	200	0	4	0	4, T_2 & T_3 upright	4	Unchanged	
	Deficient	4	175-225	0	4	0	3, T_2 & T_3 upright	2	1, T_2 & T_3 higher with high origin	
							1, flat or low	0	1, upright	
Sodium Pyruvate s.c.	Normal	6	96-150	1 (slight)	4	1 (slight)	6, T_2 & T_3 upright	5	1, T_3 flat	
	Deficient	8	100-135	2 (slight, transient)	2	6	2, upright	0	2, T_2 & T_3 higher	Before vitamin B_1
							6, T_2 or T_3 low, flat or inverted	0	6, upright or higher	
	Deficient after Vitamin B_1	3	125	0	3	0	1, upright	0	1, T_2 higher	14-21 hours after 0.015 mg. vitamin B_1
							2, flat or inverted	1	1, T_2 & T_3 upright	
Sodium Pyruvate i.v.	Normal	2	100	0	0	2	1, T_2 & T_3 upright	1	Unchanged	Ether anesthesia
							1, T_3 flat	1	Unchanged	
	Deficient	2	75-100	0	2	0	1, T_2 & T_3 upright	0	1, T_2 & T_3 slightly higher	
							1, flat or inverted	0	1, T_2 & T_3 upright	
Pyruvic Acid p.o.	Normal	7	56-182	0	4	3	7, T_2 & T_3 upright	4	2, T_2 slightly higher 1, T_2slightly lower	Few electrocardiograms in some cases
	Deficient	7	50-100	2	4	1	3, T_2 & T_3 upright	3	Unchanged	
							3, low, flat or inverted	2	1, lower	

*In terms of pyruvic acid.

TABLE III

ELECTROCARDIOGRAPHIC CHANGES IN NORMAL RATS AFTER REPEATED DOSES OF CHEMICAL SUBSTANCES

	NO. OF RATS	DOSAGE (MG. PER 100 GRAMS BODY WT.)	DURATION OF EXPERIMENT (DAYS)	NUMBER OF EXPERIMENTS AND EFFECT ON HEART RATE		NUMBER OF EXPERIMENTS AND EFFECT ON T WAVES	
				AFTER INDIVIDUAL DOSES†	DURING EXPERIMENTAL PERIOD‡	AFTER INDIVIDUAL DOSES	DURING EXPERIMENTAL PERIOD
Sodium Pyruvate p.o.	6	85-656*	16-26	13, no change 4, slight decrease	4, no change 2, slight decrease	16, no change 1, T_2 higher	6, no change
Sodium Pyruvate s.c.	2	64-151*	4-12	2, no change	1, no change 1, slight decrease	2, no change	2, no change
Pyruvic Acid p.o.	5	61-200	8-14	6, no change 4, decrease	2, no change 3, decrease	7, no change 3, T_2 or T_3 slightly higher	5, no change
Sodium Lactate p.o.	6	182-648*	18-21	6, no change 2, slight decrease	5, no change 1, decrease	8, no change	6, no change
Sodium Lactate s.c.	2	64-358*	15	Variable, few records	1, no change, variable 1, decrease	3, no change 1, T_2 & T_3 higher	2, no change
Lactic Acid p.o.	2	68-329	4-12	3, no change 1, slight increase 2, decrease Few electrocardiograms	1, no change 1, decrease	5, no change 1, T_2 slightly higher	1, no change 1, slightly lower
Methyl Glyoxal p.o.	3	100-200	10-19	6, no change 1, increase 1, decrease	2, no change 1, decrease in 1 record	8, no change	2, no change 1, slightly lower
Glyceraldehyde p.o.	3	400	15-22	7, no change 3, slight decrease	2, no change 1, slight decrease	10, no change	2, no change 1, T_3 slightly higher

*In terms of pyruvic or of lactic acid.

†Only changes of 30 beats or more are noted.

‡Only changes of 40 beats or more are noted.

Control rats which received repeated daily doses of pyruvate by mouth showed but few changes in the heart rate or in the shape of the T waves (Table III). Young control rats grew rapidly, and older rats, with one exception, maintained their weight during the administration of pyruvate. On these rats, weekly experiments were performed in which electrocardiograms were taken before, and at hourly intervals for three hours after, the administration of 200 mg. of pyruvate. The records showed only an occasional increase in the height of the T waves or a slight decrease in rate after pyruvate. Qualitative tests by a modification[14] of the method of Simon and Piaux[15] indicated that the urine contained pyruvic acid most of the time during the period that pyruvate was being administered.

One additional normal rat was fed a control diet, but was restricted to the average amount of food usually consumed by deficient rats. This rat decreased in weight, but maintained a normal heart rate. After seventeen days it was continued on the same food intake, but for 12 days received, in addition, 400 mg. of sodium pyruvate daily by mouth. The heart rate and electrocardiogram did not change significantly. The body weight continued to decrease.

Deficient rats which were receiving daily doses of sodium pyruvate by mouth rapidly increased in weight after the administration of 0.016 mg. of vitamin B_1, as did control deficient rats which were not receiving sodium pyruvate. Measurement of the food intake for a period of eight days indicated that the administration of the pyruvate solution by

TABLE IV

EFFECT ON RATS DEFICIENT IN VITAMIN B_1 OF REPEATED DOSES OF CHEMICAL SUBSTANCES

	NO. OF RATS	DOSES (MG. PER 100 GRAMS BODY WT.)	DURATION OF EXPERIMENT (DAYS)	AVERAGE NO. DAYS MAINTAINED ON 0.016 MG. VITAMIN B_1	
				CONTROL	DURING EXPERIMENT
Sodium Pyruvate p.o.	1	125-200*	13	--	11
	4	300-400*	25-43	9.5	8
Sodium Pyruvate s.c.	5	100-200*	10-15	8.5	8
Pyruvic Acid p.o.	2	50-125	9	6.5	6
Sodium Lactate p.o.	2	400*	18	6	6
Sodium Lactate s.c.	2	100-200*	13	--	--
Lactic Acid p.o.	2	200-400	10-18	7.5	6
Methyl Glyoxal p.o.	5	100-300	8-20	8.5	8.5
Glyceraldehyde p.o.	3	400	14-21	8	11

*In terms of pyruvic or of lactic acid.

stomach tube did not significantly influence the normal food intake. Two rats which were receiving pyruvate were maintained on 0.016 mg. of thiamin for a somewhat shorter time, and one for a slightly longer time, than when they were not receiving pyruvate (Table IV). Dropped beats

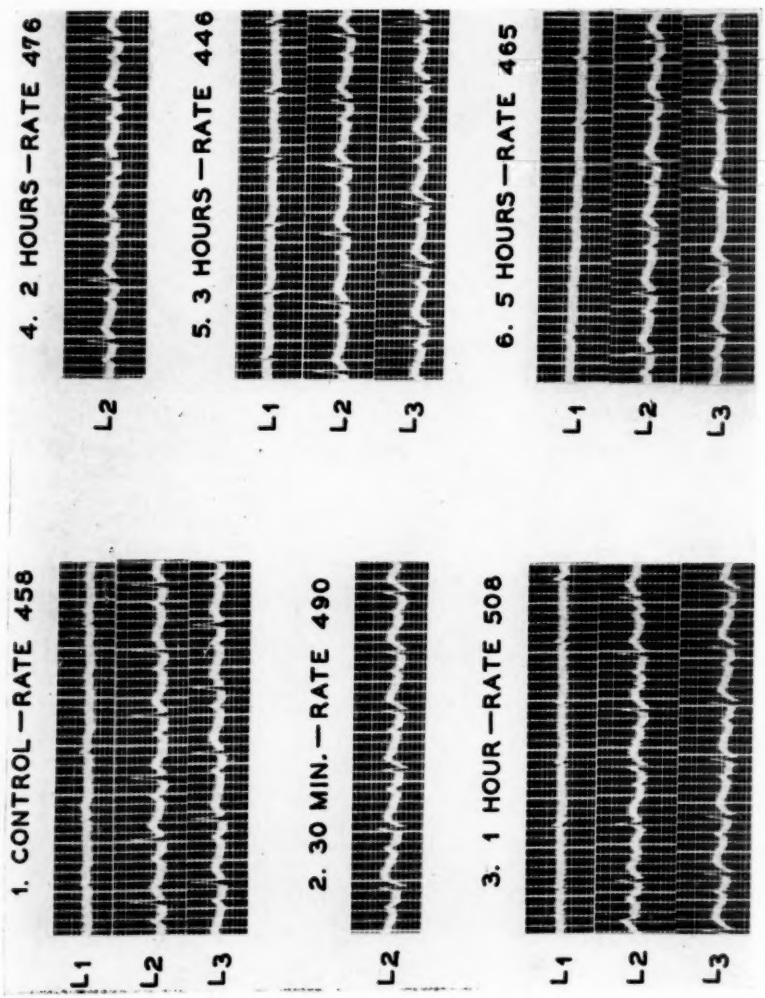

Fig. 1.—Electrocardiograms of a normal rat before and after the subcutaneous injection of 125 mg. of sodium pyruvate per 100 grams of body weight. The time lines are 1/50 second apart.

and sinoauricular block, which are seldom observed in the electrocardiograms of rats, appeared occasionally in those of three deficient rats which were receiving daily doses of pyruvate. The abnormal T waves and sinus arrhythmia which occur in vitamin B_1 deficiency appeared frequently, and the complexes varied considerably after vitamin B_1. In two rats, electrocardiographic abnormalities persisted even after frequent small doses of thiamin which brought about progressive weight gains. In these rats the electrocardiograms did not become normal for some time after pyruvate was discontinued. The pH of the urine did not differ

greatly after pyruvate (6.4 to 7.0) from that of control (6.4 to 6.8) or deficient rats (5.7 to 7.8) which had not received pyruvate.

Sodium Pyruvate, Administered Subcutaneously.—The fatal subcutaneous dose of sodium pyruvate was lower for rats deficient in vitamin B_1 (150 to 175 mg.) than for normal rats (275 to 300 mg.) (Table I). Two deficient rats which died from two and one-half to four hours after the adminstration of 150 mg. of pyruvate developed neurologic symptoms before death. Smaller single doses produced no significant changes in the electrocardiograms of normal control rats (Table II, Fig. 1). In deficient rats, sodium pyruvate was often followed by a decrease in heart rate, sometimes preceded by a temporary rise (Fig. 2). The T waves became upright, or higher, if already upright (Table II, Fig. 3). If the pyruvate was given from fourteen to twenty-one hours after the administration of thiamin, the decrease in rate after pyruvate was less marked than before thiamin, but the T waves were higher in two cases (Table II, Fig. 2). Three deficient rats were given 4 mg. of *atropine sulfate* per 100 grams of body weight, followed by 125 mg. of pyruvate. In these rats the rate remained unchanged, but the T waves were higher

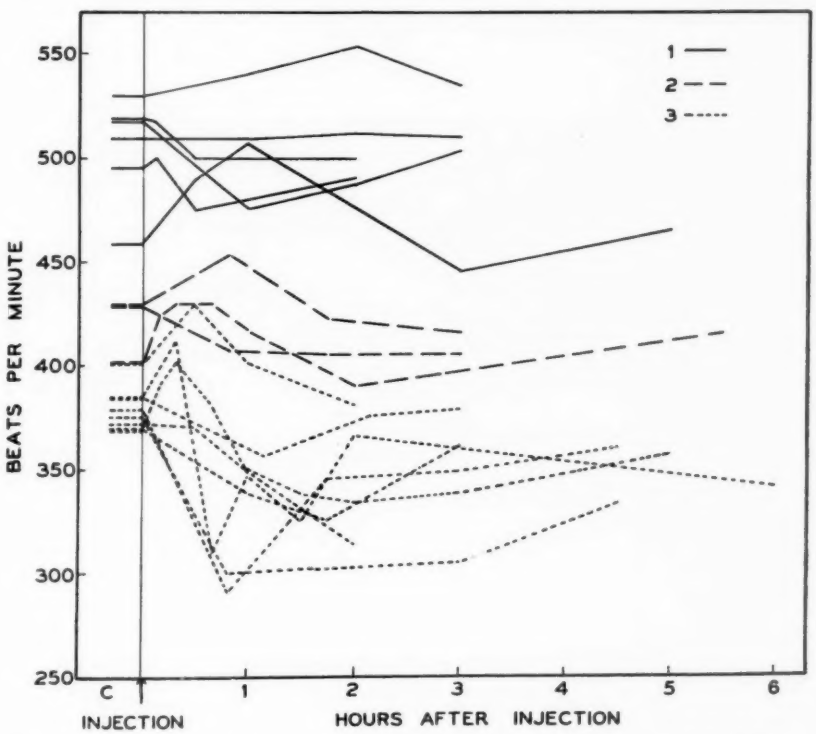

Fig. 2.—Effect on heart rate of the subcutaneous injection of from 96 to 150 mg. of sodium pyruvate per 100 grams of body weight. Results have been plotted on (*1*) normal rats, (*2*) rats on a diet deficient in vitamin B_1 which had received thiamin seventeen to twenty-one hours previously, and (*3*) rats on a diet deficient in vitamin B_1.

in one case, indicating that the fall in heart rate usually observed after pyruvate, but probably not the T-wave changes, is caused by vagal stimulation.

Tables III and IV summarize the effects of repeated, small, daily doses of sodium pyruvate, injected subcutaneously into control and deficient rats. While receiving pyruvate, the majority of the deficient rats with low or flat T waves did not show any change in the T waves after the doses of vitamin B_1 which they received. Since few other significant changes were observed, and since repeated subcutaneous injections of pyruvate caused considerable local irritation in the rats, no further experiments were performed.

Sodium Pyruvate, Administered Intravenously.—The fatal dose was not determined, but one control rat died after 121 mg. had been injected.

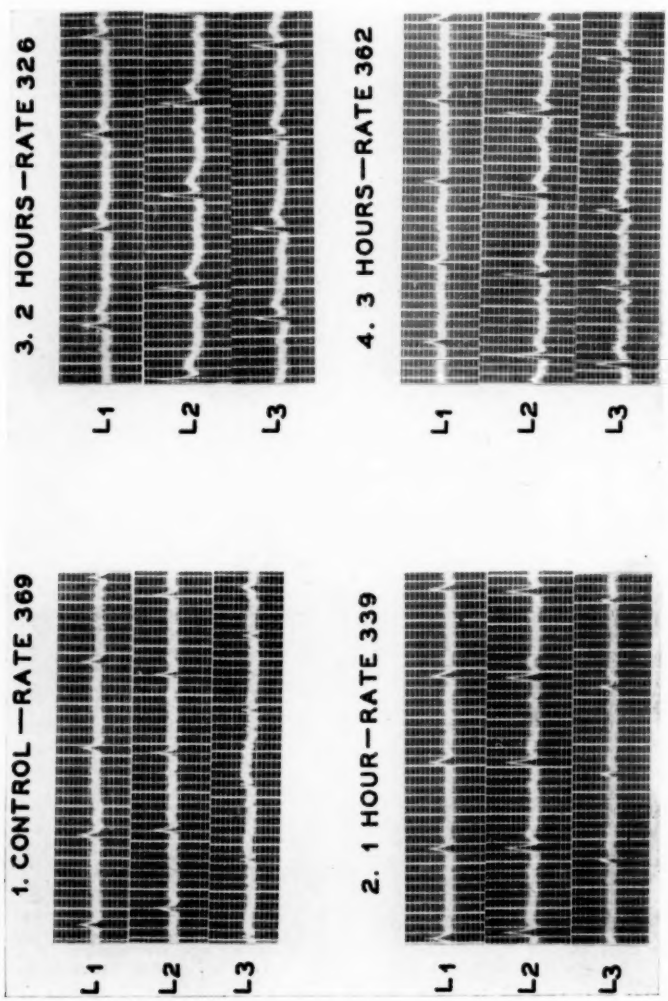

Fig. 3.—Electrocardiograms of a deficient rat before and after the subcutaneous injection of 100 mg. of sodium pyruvate per 100 grams of body weight. The time lines are 1/50 second apart.

Two control rats which were receiving 100 mg. showed a decrease in heart rate and a slight increase in the P-R interval (Table II). In two deficient rats the T waves were slightly higher from five to twenty-five minutes after the injection (Table II). No other changes were noted in this small series.

Pyruvic Acid, Administered Orally.—The fatal dose for normal and deficient rats was approximately 300 to 350 mg., but smaller doses sometimes had an injurious effect on the digestive or the respiratory system, which later led to death (Table I). The effect of single smaller doses of pyruvic acid is summarized in Table II. The changes noted were probably not significant. Normal rats which were receiving daily doses of pyruvic acid had slower heart rates, in several cases, within a few hours after the administration of the drug, as well as a lowered rate level at the end of the period of treatment (Table III). Tests showed that the urine contained pyruvic acid for only a few hours after it was given. Considerable difficulty was experienced in giving pyruvic acid by stomach tube, for small amounts in the throat proved very irritating, and a number of rats died with respiratory symptoms after receiving pyruvic acid for several days. In deficient rats which were receiving repeated doses of pyruvic acid (Table IV), the body weight did not increase readily after the administration of vitamin B_1.

These results with sodium pyruvate and pyruvic acid indicate that deficient rats are somewhat more sensitive to sodium pyruvate than normal rats, for the fatal dose, as well as the dose causing cardiac changes, was lower for deficient rats. The changes produced consisted mainly in an increase in the height of the T waves and a slight decrease in heart rate, especially after subcutaneous and intravenous injection of sodium pyruvate. It will be noted later that T-wave changes similar to those produced by sodium pyruvate were produced in some cases by sodium bicarbonate and sodium lactate, and might have been caused, in part, by alkalosis. The P-R interval usually showed no definite alteration after pyruvate, but was increased in a few cases. As previously noted,[1] P waves were regularly present in deficient rats, but were often lower than in normal rats. The P waves were unaffected by pyruvic acid or other metabolites. The Q-T interval is difficult to measure in deficient rats because of the shape of the T waves, but in some cases its duration increased after pyruvate. In two rats, continued administration of large doses of pyruvate tended to increase their thiamin requirement slightly. To what extent the requirement may have been increased as a result of the increase in metabolism caused by forced feeding is uncertain. Two deficient rats which were receiving repeated doses of pyruvate had abnormal T waves or a slow heart rate, which returned to normal only after frequent doses of thiamin. Two rats which had been deficient for some time, either when they were, or were not, receiving pyruvate, developed permanent neurologic symptoms.

Lactic Acid ($CH_3.CHOH.COOH$)

An accumulation of lactic acid in the blood,[4, 16, 17, 18] as well as in the muscle, liver, and heart,[19, 20] of deficient animals is one of the chemical features of vitamin B deficiency. In man, the lack of vitamin B leads to a disturbance in the resynthesis of glycogen from lactic acid.[21] A number of observations have been made on the effect of administering lactic acid or lactate to animals or man. According to Kalaja and Närvanen,[13] lactic acid, when injected subcutaneously in rats in an amount equal to 50 per cent of the lethal dose, decreased the heart rate by about 33 per cent for a period of several hours. The effect on rabbits and pigeons was hardly discernible. Guha[22] found that the ingestion of sodium lactate did not appreciably hasten the appearance of symptoms in rats deficient in vitamin B_1 but that the lethal dose of lactate injected subcutaneously was less for deficient than for normal animals. In Schrader's experiments on rats, lactic acid in the diet did not hasten the onset of symptoms.[11, 23] Lecoq[24, 25] observed that the addition of lactic acid to the diet of pigeons caused them to develop polyneuritis sooner, and prevented the utilization of increased amounts of vitamin B. Hayasaka[26] injected sodium lactate intravenously in man, and observed a higher level of lactic acid in beriberi patients than in normal subjects.

Sodium Lactate, Administrated Orally.—The fatal dose of sodium lactate when given by mouth was not less for deficient rats (over 700 mg.) than for normal rats (500 to 700 mg.) (Table I). The results of giving smaller single doses of lactate by mouth are summarized in Table V. No consistent changes were demonstrated in normal or in deficient rats, although a certain number of changes in the heart rate or in the height of the T waves occurred in both groups after giving lactate. In three cases, T waves became upright or higher.

Three out of four full-grown, normal rats which received daily doses of lactate by mouth for several weeks showed a decrease in weight (16 to 29 grams); two young rats showed a normal increase in weight. No definite changes in the heart rate or electrocardiographic complexes were seen in the control animals (Table III). Two deficient rats received lactate by mouth for eighteen days without a marked decrease in the time required to become deficient (Table IV). The heart rate responded to thiamin, in spite of the administration of lactate.

Sodium Lactate, Administered Subcutaneously.—The fatal dose of sodium lactate, when injected subcutaneously, was not less for deficient rats (over 450 mg.) than for normal rats (350 to 400 mg.) (Table I). The results of giving single, nonfatal doses are recorded in Table V. In control rats the larger doses produced symptoms of weakness and, in two out of eight cases, a decrease in heart rate. In the majority of cases the rate did not change, and no significant changes in the electro-

cardiograms occurred, even after the fatal doses. Experiments on deficient rats did not show consistent alterations in the T waves, either before, or from seventeen to eighteen hours after, giving thiamin (Table V). In approximately half of the deficient rats the heart rate decreased after lactate.

Two control rats received daily doses, with the variations noted in Table III. The speed with which two deficient rats lost weight was not noticeably affected by the continued administration of lactate, and the rats did not become deficient for at least ten days after receiving 0.020 mg. of thiamin.

Sodium Lactate, Administered Intravenously.—The two control rats which received sodium lactate intravenously showed a decrease in heart rate of approximately 75 beats per minute, about ten minutes after the intravenous injection of nonfatal doses of sodium lactate (Table V). The P-R interval increased in one case. In two deficient rats the rate did not change significantly, but the T waves, which were low or flat, became upright, or higher, after lactate was given (Fig. 4).

Lactic Acid, Administered Orally.—There was no significant difference between the fatal dose for normal rats (approximately 550 mg.) and that for deficient rats (over 500 mg.) (Table I). After smaller doses, normal and deficient rats showed no striking or consistent changes (Table V). The continued administration of lactic acid to two control rats produced a slower heart rate and slightly lower T waves, in one case, near the end of the period (Table III). Of two deficient rats which were receiving daily doses of lactic acid, one was maintained for a slightly shorter period on a given dose of thiamin than might have been expected if it had not been receiving lactic acid (Table IV). The weights and T waves of these rats responded to thiamin.

The results of administering sodium lactate and lactic acid indicate that deficient rats are probably not more sensitive than normal rats to sodium lactate. Electrocardiographic and weight changes similar to those observed after giving pyruvate may occur in some cases, but they are less definite and consistent. Large doses of lactate sometimes decreased the heart rate, especially when given intravenously, but appeared to have little effect on the rate or T waves in many cases. The P-R interval was increased after giving lactate in a few cases, but usually showed no definite change. The electrocardiograms of one deficient rat, which was given sodium lactate subcutaneously, are of interest because they show the extent of the cardiac abnormalities which may occur. Before giving lactate the rate was 395, and T_2 and T_3 were upright. Three hours after administering 153 mg. of lactate, this rat had flat or diphasic T waves and a prolonged P-R interval; after 4 hours the rat showed marked weakness, a totally irregular heartbeat (rate approximately 280), with occasional ectopic ventricular beats, and no discernible P waves.

TABLE V

ELECTROCARDIOGRAPHIC CHANGES IN RATS AFTER SINGLE DOSES OF SODIUM LACTATE AND LACTIC ACID

	NUTRITIONAL STATE	NO. OF RATS	DOSAGE* (MG. PER 100 GRAMS BODY WT.)	EFFECT ON HEART RATE			NUMBER OF RATS AND EFFECT ON T WAVES			REMARKS
				INCREASE	NO CHANGE	DECREASE	INITIAL FORM OF T WAVES	NO CHANGE	FORM OF T WAVES AFTER ADMINISTRATION OF SUBSTANCE	
Sodium Lactate p.o.	Normal	3	250-300	1	2	0	2, T_2 & T_3 upright 1, T_3 flat	1 0	1, T_2 & T_3 higher 1, T_3 upright	
	Deficient	7	200-250	1	5	1 (slight)	4, upright 3, low or flat	3 2	1, low or flat 1, T_1 slightly higher	
Sodium Lactate s.c.	Normal	8	100-200	1	5	2	8, T_2 & T_3 upright 1, low origin	8	Unchanged	
	Deficient	9	100-156	2 (slight)	3	4	2, T_2 & T_3 upright 1, variable 6, low, flat or inverted	1 4	1, T_2 slightly higher 1, flat 2, T_3 upright	Before vitamin B_1
	Deficient after Vitamin B_1	4	125	3 (slight, transient)	1	0	3, upright 1, flat	1 1	1, T_3 slightly lower 1, variable Unchanged	17 to 18 hours after 0.015 mg. vitamin B_1
Sodium Lactate i.v.	Normal	2	100-125	0	0	2	2, upright	2	Unchanged	Ether anesthesia
	Deficient	2	100-150	1 (slight)	1	0	2, low, flat or inverted	0	2, upright or higher	
Lactic Acid p.o.	Normal	6	100-165	0	4	2 (slight)	6, T_2 & T_3 upright 1, T_3 low	5	1, T_1 higher; T_3 diphasic	
	Deficient	4	100-150	1 (transient)	3	0	2, upright 1, T_2 & T_3 slightly high 2, flat	2 2	Unchanged Unchanged	

*In terms of lactic acid.

Vitamin B_1 was given immediately, and seven hours later the heartbeat was still irregular, but the rate had increased to approximately 500. The electrocardiogram later became normal.

Sodium Bicarbonate and Ammonium Chloride

Because of the possibility that the electrocardiographic changes after giving pyruvic or lactic acid, or their salts, were caused by the administration of large amounts of sodium, or by changes in the acid-base balance, control experiments were performed with sodium bicarbonate and ammonium chloride. Barker, Shrader, and Ronzoni[27] reported that, in normal human subjects, alkalosis, produced by hyperventilation or by the ingestion of sodium bicarbonate, was accompanied by flattening or inversion of the T waves, whereas acidosis, produced by exercise or by the ingestion of ammonium chloride, was accompanied by an increase in the amplitude of the T waves. Wilkins, Weiss, and Taylor[12] also found

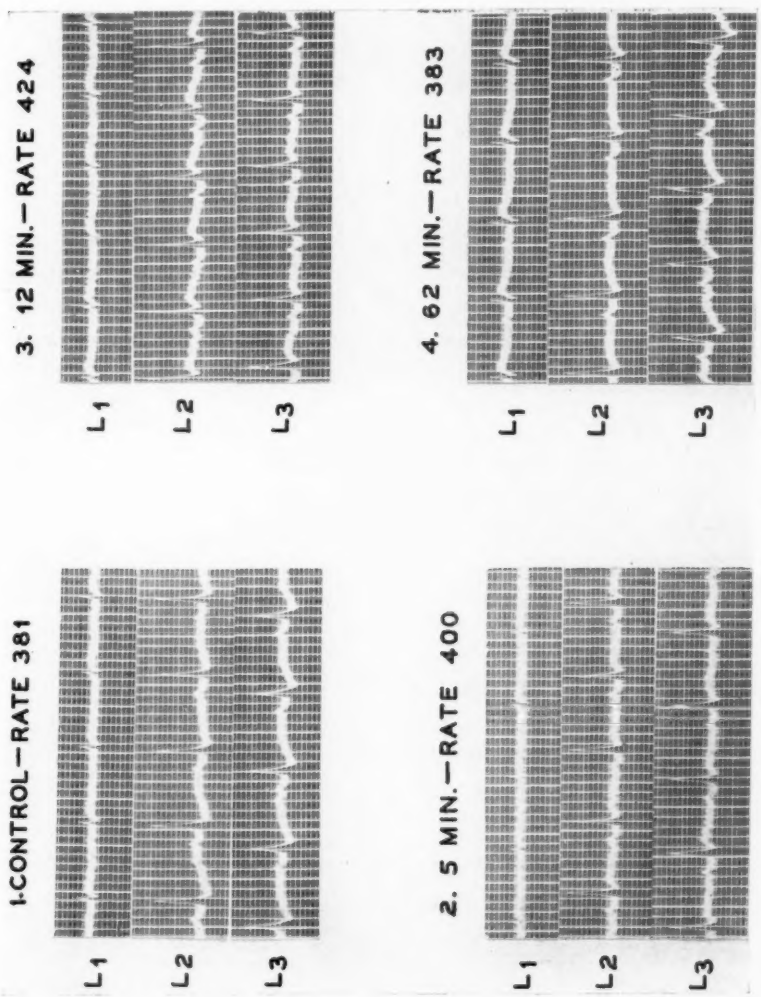

Fig. 4.—Electrocardiograms on a deficient rat before and after the intravenous injection of 100 mg. of sodium lactate per 100 grams of body weight. The time lines are 1/50 second apart.

that the electrocardiographic changes after giving sodium bicarbonate were qualitatively the same as, but usually quantitatively less than, those produced by comparable amounts of sodium pyruvate. Guha[22] observed that ammonium chloride (100 to 222 mg. per 100 grams of body weight) was more toxic than sodium lactate, and apparently equally fatal to normal and vitamin B_1 deficient rats. We used doses of sodium bicarbonate which were comparable in sodium content to 200 mg. doses of sodium pyruvate (calculated as pyruvic acid).

The oral administration of single doses of 180 to 200 mg. of sodium bicarbonate per 100 grams of body weight to two control rats increased the heart rate very slightly in one instance. There was a slight increase in the height of T_1 in one rat, and of T_2 and T_3 in the second animal. In nine experiments deficient rats received from 100 to 200 mg. by mouth, after which the heart rate increased slightly in three instances. In three out of six rats with flat or inverted T waves, T_2 or T_3 became upright or had a slightly higher origin after bicarbonate. After 200 mg. the pH of the urine increased from 6.8 to 9.0, where it remained for at least four hours. The continued administration of sodium bicarbonate by mouth (190 to 270 mg. per day) to three deficient rats for eighteen to twenty-eight days did not change the speed with which they became deficient. The heart rate was unchanged by bicarbonate. In two of the rats, during the first few days of sodium bicarbonate administration, T_2 changed from a flat or inverted wave to an upright one after sodium bicarbonate was given (Fig. 5). The pH of the urine usually increased to 9. It should be noted that sodium bicarbonate had a more marked effect on the acid-base balance than did sodium pyruvate, for doses of 400 mg. of bicarbonate per day rapidly caused tetany in rats, whereas similar doses of pyruvate could be given for an extended period without apparent effect.

The subcutaneous injection of sodium bicarbonate in seven deficient rats and one control rat had no effect on the heart rate. Doses of 115 to 138 mg. of sodium bicarbonate had no definite effect on the electrocardiographic complexes, whereas doses of 200 mg. produced higher T waves in all three of the deficient rats to which they were given. In some of the early experiments the sterile bicarbonate solution was not freshly prepared.

The effect of ammonium chloride (50 to 200 mg.) was studied in six normal and four deficient rats. In normal rats the heart rate was slowed in all but one case, but the T waves were usually not changed. In deficient rats the results on the rate were variable, whereas the T waves were not affected by ammonium chloride.

Methyl Glyoxal ($CH_3.CO.CHO$)

Methyl glyoxal has been found in the blood, urine, and spinal fluid in a few cases of oriental beriberi,[3] as well as in the urine of infants with

various pathologic conditions,[5] including "acute toxic dyspepsia," which may be a manifestation of vitamin B_1 deficiency.[6] Methyl glyoxal has been found in the urine of vitamin B_1 deficient polyneuritic dogs and rats, but in rats it is claimed not to be specific for B_1 avitaminosis.[28] Simola[29] was not able to detect the presence of methyl glyoxal in the urine of rats deficient in vitamin B. Jansen and Westenbrink[30] do not consider it probable that methyl glyoxal intoxication causes polyneuritis. Takamatsu and Sato[31] found that the hearts of rabbits deficient in vitamin B became enlarged after the intravenous and oral administration of methyl glyoxal. The enlargement following the administration of methyl glyoxal was less when vitamin B was given. Ariyama,[32] however, did not observe that intravenous injections had any effect on rabbits, or on the speed with which polyneuritis developed in pigeons.

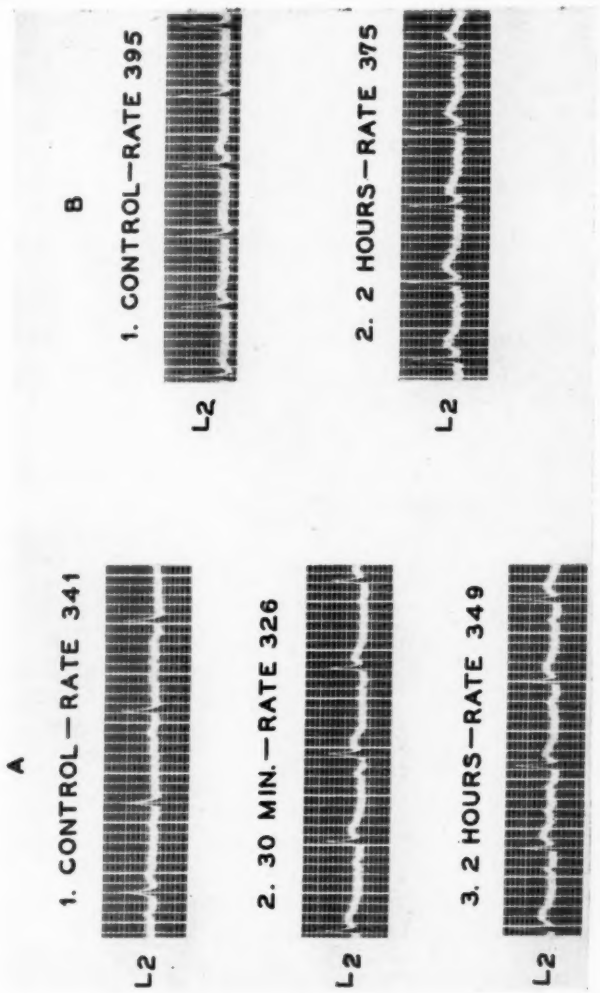

Fig. 5.—Electrocardiograms of two deficient rats before and after the oral administration of 100 mg. of sodium bicarbonate per 100 grams of body weight. The records in *A* were taken before vitamin B_1 was given; those in *B* were taken two days after giving 0.016 mg. of thiamin.

In normal dogs and rabbits, large doses of methyl glyoxal have been found by Martini,[33, 34] and by Goldenberg, Gottdenker, and Rothberger,[35] to act on the vagus center, causing a decrease in heart rate, a fall in blood pressure, and cardiac dilatation. Goldenberg and his co-workers[35] observed changes in the S-T segment, sinus arrhythmia, intramuscular conduction disturbances, and A-V block in the dog's electrocardiogram, as well as a widening of the coronary vessels.

For the experiments to be reported here, solutions of methyl glyoxal were prepared daily from 20 per cent aqueous stock solutions.* The latter were obtained at intervals of several weeks, in order to avoid the possibility of decomposition. The stock solution was a clear, colorless liquid, acid to litmus.

Methyl Glyoxal, Administered Orally.—The fatal dose of methyl glyoxal by mouth was not less for deficient rats (over 200 mg.) than for normal rats (175 to 200 mg.) (Table I). The cardiac changes after single doses of methyl glyoxal (100 to 200 mg.) appear in Table VI. Electrocardiograms were taken on four additional control rats, which received fatal doses of 175 to 300 mg. In normal and in deficient rats no marked changes in the T waves took place for three hours, even after fatal doses; the heart rate decreased somewhat in several cases. It should be noted that Stöhr[36] observed a rise in the liver glycogen within three hours after giving methyl glyoxal by mouth, indicating that it was absorbed during this period.

Three control rats ate less food while receiving daily doses of methyl glyoxal. Two rats lost a small amount of weight, whereas the third lost considerable weight, showed a decrease in heart rate, and died after thirteen days. Daily doses of methyl glyoxal did not affect the electrocardiographic complexes during the period of administration (ten to nineteen days) (Table III). No neurologic manifestations were observed. The sensitivity of control rats to methyl glyoxal is shown by the fact that a fourth rat died after three daily doses of 100 to 150 mg.

While they were receiving repeated doses of methyl glyoxal by mouth, deficient rats responded normally to thiamin (Table IV). Early in the period of administration, three rats were maintained on a given dose of vitamin B_1 for a somewhat shorter time than might have been expected without methyl glyoxal; after longer administration of methyl glyoxal, however, two of the rats appeared to need no thiamin while they were receiving methyl glyoxal. The significance of this is not clear.

Methyl Glyoxal, Administered Subcutaneously.—Methyl glyoxal was found to be absorbed with difficulty from the subcutaneous tissues. Of two normal rats which received 150 and 100 mg., respectively, the first developed marked swelling and was dead the next day, whereas the second had marked swelling for some days, and then developed a slough.

*Prepared by Macmillan and Cleveland, Chemists, Chicago.

TABLE VI

ELECTROCARDIOGRAPHIC CHANGES IN RATS AFTER SINGLE DOSES OF METHYL GLYOXAL AND GLYCERALDEHYDE

	NUTRITIONAL STATE	NO. OF RATS	DOSAGE (MG. PER 100 GRAMS BODY WT.)	EFFECT ON HEART RATE			NUMBER OF RATS AND EFFECT ON T WAVES			REMARKS
				INCREASE	NO CHANGE	DECREASE	INITIAL FORM OF T WAVES	NO CHANGE	FORM OF T WAVES AFTER ADMINISTRATION OF SUBSTANCE	
Methyl glyoxal p.o.	Normal	3	100-200	0	1	2 (slight)	3, T_2 & T_3 upright	3	Unchanged	
	Deficient	7	107-200	1 (slight)	4	2 (slight)	7, T_2 & T_3 upright	6	1, T_2 & T_3 slightly lower	
Methyl glyoxal i.v.	Normal	2	24-50	0	1	1 (transient)	2, T_2 & T_3 upright	2	Unchanged	Ether anesthesia; rate varies with anesthesia
	Deficient	2	30-42	0	0	2	2, T_2 & T_3 upright	0	2, T_2 & T_3 higher	
Glyceraldehyde p.o.	Normal	3	200-250	0	1	2	3, T_2 & T_3 upright; T_3 low	3	Unchanged	
	Deficient	5	200	0	4	1	2, T_2 & T_3 upright 3, T_2 & T_3 flat	1 2	1, T_2 & T_3 higher 1, T_2 & T_3 higher	T-waves higher with excitement
Glyceraldehyde i.v.	Normal	2	55-75	0	1	1	1, T_2 & T_3 upright 1, T_3 flat or inverted	1 1	Unchanged Unchanged	
	Deficient	2	50	0	2	0	1, upright 1, flat	0 1	1, T_2 & T_3 slightly lower Unchanged	

The only change in the electrocardiograms in the first three hours was an increase in the heart rate in one rat.

Methyl Glyoxal, Administered Intravenously.—Experiments in which methyl glyoxal was injected intravenously are summarized in Table VI. On control rats, records were taken immediately after injection, and, on deficient rats, during and after injection. Normal, as well as deficient, rats may be killed by very small quantities of methyl glyoxal if it is injected rapidly. As the rate of injection was increased until it approached the fatal dose, electrocardiographic changes which are typical in moribund animals appeared, that is, a greatly decreased heart rate and increase in the height of the T wave. The rats recovered rapidly, however, when the injection was stopped. Methyl glyoxal is probably quickly removed from the blood stream by the liver, for Martini[34] found it to be ineffective when injected into the portal circulation. Deficient rats which had received methyl glyoxal recovered satisfactorily after thiamin, and showed no permanent cardiac damage.

The differences in the response of normal and of deficient rats to methyl glyoxal are, therefore, not striking. The fatal dose of methyl glyoxal is small for normal rats. This substance is known to be easily removed from the blood,[34] and changes were seen in the electrocardiograms only during intravenous injection of almost fatal doses.

Glyceraldehyde ($CH_2OH.CHOH.CHO$)

Although glyceraldehyde has not been shown, as far as we know, to be definitely linked with vitamin B_1 deficiency, it was decided to study its effect on deficient rats because it may possibly be an intermediary triose in the breakdown of glucose to lactic acid. Reeves[37] has shown that glyceraldehyde is toxic to the normal rabbit heart, but is efficient in maintaining the rhythmic contractions of the excised amphibian heart. Glyceraldehyde also protects the frog heart against the toxic action of potassium cyanide.[38]

The glyceraldehyde used in the present investigation was a Schering-Kahlbaum product* which was obtained as a powder in 5-gram ampules. With slight heating, it was sufficiently soluble in water to make a 10 per cent solution. A fresh solution was made up for each experiment.

Glyceraldehyde, Administered Orally.—The fatal dose was not determined. Two control rats received 500 and 600 mg., respectively, and two deficient rats received 400 and 600 mg., respectively, without marked symptoms (Table I). The heart rate of the deficient rat which received 400 mg. was decreased forty beats a minute, but the complexes were not significantly affected. After smaller, single doses, few marked changes in the rate or T waves were observed in normal or deficient rats. The heart rate decreased in three out of eight cases (Table VI).

Throughout a period of two to three weeks, young control rats received daily doses of glyceraldehyde by mouth, during which time they

*Obtained from Akatos, Inc., New York.

grew and ate well, although their increase in weight may have been slightly less than that of controls which did not receive glyceraldehyde. The heart rate showed no significant decrease, and the T waves were unchanged (Table III). During the continued administration of glyceraldehyde to deficient rats, the T waves and heart rate responded to thiamin, and the rats appeared to be maintained on a given dose of thiamin as long as when they were not receiving glyceraldehyde (Table IV). One rat was maintained somewhat longer while receiving glyceraldehyde. In order to rule out the possibility that the glyceraldehyde solution was a source of vitamin B_1, two deficient rats were given daily doses of autoclaved glyceraldehyde. During the period of observation (seven to ten days), no apparent difference was observed in the responses of these animals as compared with those which received nonautoclaved glyceraldehyde.

Glyceraldehyde, Administered Subcutaneously.—Glyceraldehyde, like methyl glyoxal, was found to be absorbed with difficulty from the subcutaneous tissues. Two control rats received 300 mg. apiece and were dead within twenty-four hours. One deficient rat and one normal rat received 100 mg. apiece, after which they developed marked swelling, followed by sloughing. The electrocardiograms showed either no change, or a slight decrease in the heart rate and a slight increase in the height of the T waves (two cases).

Glyceraldehyde, Administered Intravenously.—The results are summarized in Table VI. No marked or consistent changes in heart rate or electrocardiographic complexes were observed in the small number of experiments performed.

In summary, the differences in results on normal and on deficient rats after the administration of glyceraldehyde were not striking.

Glucose ($CH_2OH.(CHOH)_4.CHO$)

Numerous observations have been reported on the relation of the vitamin B requirement to the intake of carbohydrate. McCarrison[39] has shown that a high carbohydrate diet hastens the symptoms of deficiency. Lepkovsky, Wood, and Evans[40] found that the glucose tolerance curves of rats were high only when the animals became severely deficient. The observations of Nitzescu and Benetato,[41] and of Kauffman-Cosla, Vasilco, and Oeriu,[42] indicate that there is a decrease in glucose tolerance in B avitaminosis. Guha[22] has discussed the literature, and reported that the vitamin B_1 requirement is independent of the protein-carbohydrate ratio, or the nature of the carbohydrate in the diet. Cowgill[43] points out the importance of the total caloric intake.

It was decided to supplement and control our experiments on intermediary carbohydrate metabolites by cardiac studies after the continued administration of glucose to rats. One series of four deficient rats received glucose subcutaneously (0.67 to 1.80 grams daily) from the twenty-first to the fiftieth day of their first deficiency; another series

of three rats, after a number of previously induced vitamin B_1 deficiencies, received glucose subcutaneously (0.91 to 1.23 grams daily) for fifteen days, then by mouth (1.26 to 1.85 grams) for an additional thirty-three to thirty-five days. The glucose contained no vitamin B_1, as indicated both by the method of Meiklejohn*[44] and by the fact that autoclaved glucose was used during part of the period. Using the heart rate as a criterion, two rats of the first series became deficient for the first time a little sooner (thirty-fourth to thirty-eightieth day on the deficient diet) than control deficient rats (fortieth to forty-sixth day). One rat of the second series also was less able to maintain its body weight after long-continued glucose administration than normal rats. When rats which were receiving glucose became deficient, their heart rates slowed, and the T waves often became flat or inverted, like those of the control deficient rats. The rats quickly recovered a normal rate and had upright, or even high, T waves after thiamin was given. Single doses of glucose had no consistent effect on the heart rate or the height of the complexes, but caused an increase or decrease in one or two cases.

Adenylic Acid

A relation between adenylic acid and the cardiac effects of vitamin B_1 deficiency might be expected, for this acid is involved in muscle metabolism and the oxidation of lactic acid,[45] and also has a definite effect on the heart, causing a decrease in heart rate, impairment of auriculoventricular conduction, and lowering of the blood pressure.[46] Drury, Harris, and Maudsley[47] obtained evidence that the bradycardia of vitamin B_1 deficient rats is not prevented by the injection of barium, as are the bradycardia and heart block produced by adenosine and muscle adenylic acid.[46] More recently, however, Birch and Mapson[48] stated that the bradycardia produced in the rat by certain adenine compounds apparently resembles that of B_1 avitaminosis, and that in both cases the auricular waves disappear at low heart rates. It was also shown by these investigators that rats deficient in vitamin B_1 showed a sensitivity to these compounds, and that their cardiac tissue had a low deaminase activity, which returned to normal after vitamin B_1 was given. Kalaja and Närvanen[13] observed that subcutaneous injections of yeast adenylic acid in rats caused a profound slowing of the heart rate which was not affected by atropinization. The action of adenylic acid was relatively slight in pigeons and rabbits.

Sodium Adenylate, Administered Subcutaneously.—In the present work the fatal dose was not determined, but it is known that adenylic acid and adenosine are relatively nontoxic, and that they are not cumulative in action.[46]

In both control and deficient rats, single doses of sodium adenylate, given subcutaneously, caused no symptoms except a marked, rapid,

*Information on the vitamin B_1 content of the glucose solutions was supplied by Dr. A. P. Meiklejohn.

and transient fall in heart rate. The rate often became very slow, reaching levels seldom seen without adenylate, except when the rats were moribund. Increasing the doses from 5 to 20 mg. was not followed by progressively greater decreases in rate, but 3 mg. gave a smaller and less definite decrease. In most cases the decrease in rate was similar in control and deficient rats, both before and after thiamin (Fig. 6). Two control rats, however, showed only a slight decrease after 10 mg. The difference in dosage and method of injection may account for our failure to obtain the differences between control and deficient rats described by Birch and Mapson.[48] Two deficient rats, which were receiving 10 mg. of sodium adenylate, showed a marked decrease in heart rate even after 4 mg. of atropine. In rats, as in dogs,[46] the decrease in rate is apparently not of vagus origin. The T waves of control rats were unaffected by adenylate. Out of ten experiments on deficient rats, the T waves were somewhat higher in two, and flatter in one, after the various doses of adenylate. Inverted P waves were present in the records of three control and two deficient rats from five to sixty minutes after 5 mg. of adenylate, as well as in several records after larger doses. In a few cases, inverted P waves also appeared in the records of deficient rats which did not receive adenylate. The Q-T interval increased in some instances after giving adenylate.

Single oral or intravenous doses of adenylate or adenylic acid, or repeated daily doses, were not used except in the case of two control rats

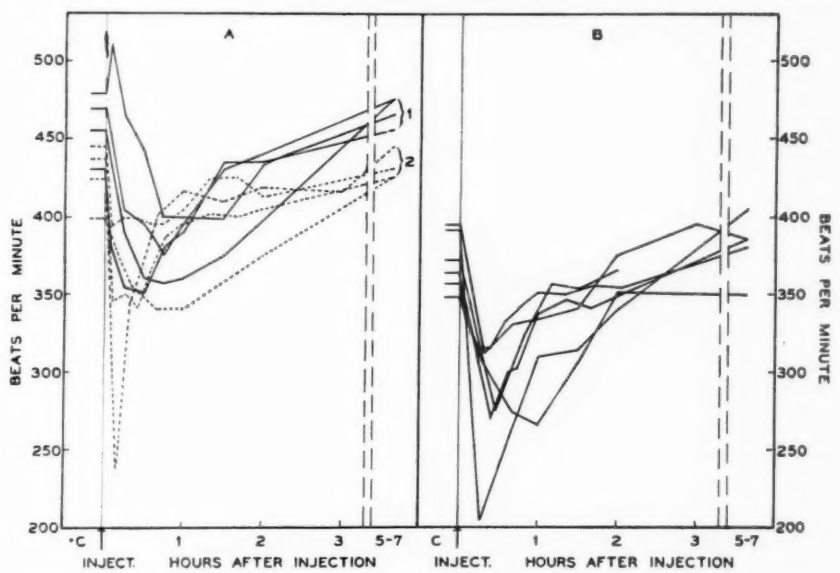

Fig. 6.—Effect on heart rate of the subcutaneous injection of 5 mg. of sodium adenylate per 100 grams of body weight. The average control levels of the heart rates before injection are indicated in column *C*. The graph on the left (*A*) shows the results on (*1*) normal rats and (*2*) rats on a diet deficient in vitamin B_1 which had received thiamin from seventeen to twenty-one hours previously. The graph on the right (*B*) shows the results on rats on a diet deficient in vitamin B_1.

which received large single oral doses of adenylate. These showed moderate slowing of the heart rate, but no change in the electrocardiogram.

Effect of Large Doses of Thiamin on Nondeficient Rats and Dogs

In a previous study[49, 50, 51] on normal persons and on patients with various types of heart disease and edema, we concluded that vitamin B_1 exerts a cardiovascular effect only in the presence of specific deficiency. In view of the work of Tislowitz and Pines[52] on normal dogs, in which they found bradycardia and marked arrhythmia after intravenous injection of thiamin, it is of interest to report here our results with large doses of the vitamin in dogs and rats. After numerous control electrocardiograms, three normal, unanesthetized dogs were followed for periods of four to ten days, during which they received single, daily, intravenous injections of 0.016 to 0.39 mg. of thiamin per 100 grams of body weight, or a total dose of from 2 to 50 mg. per animal. In all cases the heart rate decreased about 40 beats per minute during this period. The dog's heart rate, however, was found to be too variable, both as to the control level and in response to thiamin, to draw any conclusions concerning the decreases in heart rate after thiamin; furthermore, any changes produced were often not reproducible. Short experiments were also performed, in which each dog received from 0.085 to 0.403 mg. of thiamin per 100 grams (10 to 50 mg. per animal) intravenously under chloralose anesthesia. Because of the variations in rate, it was necessary to repeat each experiment with chloralose and saline as a control. In all cases thiamin lowered the rate slightly more than did saline. Two dogs showed marked sinus arrhythmia. The variation in the intervals between beats was often greater at the lower rates, irrespective of whether or not the dog was receiving thiamin.

Single doses of from 0.46 to 2.32 mg. of thiamin per 100 grams of body weight, given subcutaneously, repeatedly exerted no effect on the electrocardiograms of four normal rats; in only one instance was there a decrease in heart rate. Molitor and Sampson[53] found that the heart rate of normal rats was unchanged after intravenous injections of 1.0 mg. of vitamin B_1 per 100 grams. They also report that the lethal dose for rats is 25 mg., thus indicating the enormous difference between therapeutic and lethal doses.

Electrocardiograms on Rats Deficient in Vitamins Other Than Vitamin B_1

During this study we had the opportunity* of recording electrocardiograms on several very young rats which were deficient in vitamins other than vitamin B_1. Four rats with symptoms of riboflavin deficiency had rates of 440 to 550. In one rat the T waves were slightly higher

*We wish to express our appreciation to Dr. Otto A. Bessey for allowing us to take electrocardiograms on his rats.

than those of control rats of the same age. Three of the rats were restudied ten days later, while still deficient in riboflavin, with the same results. One rat which was deficient in vitamin B_6 had a heart rate of 380 and a rather high T_2 and T_3. One older rat, which was deficient in vitamin A, had a normal electrocardiogram and a rate of 510. The lack of vitamin B factors other than vitamin B_1 may produce a slight increase in the height of the T waves, although apparently not the flattening or inversion which may occur in vitamin B_1 deficiency. It is of interest to note that in the present series of rats, which were kept on diets containing yeast which was somewhat less strenuously treated, and thus contained slightly more riboflavin than that previously used,[1] the appearance of high T waves in the first deficiency was more rare; the changes usually consisted of flattening or inversion. With unstandardized leads, Drury, Harris, and Maudsley[47] have previously observed that, in rats, vitamins A and D exert no characteristic influence on heart rate or conduction, nor on the T waves.

DISCUSSION

This study indicates that large doses of the metabolites which were investigated fail to produce, in normal rats, manifestations characteristic of vitamin B_1 deficiency. Deficient rats which received large doses of these compounds usually did not show striking cardiac changes, or develop symptoms of deficiency earlier. The only possible exception was sodium pyruvate. In view of the fact that the amount of pyruvate administered was out of proportion to the concentration present in the body in vitamin B_1 deficiency, it is questionable whether the reduction in the heart rate and changes in the electrocardiographic complexes which were observed in deficient animals have any physiologic significance. In agreement with observations made on normal and deficient human beings,[12] the electrocardiographic changes after the administration of massive doses of sodium pyruvate were not striking. Similarly, nervous symptoms were seldom precipitated by sodium pyruvate. The results reported are in harmony with Peters' view that the acute nervous symptoms of vitamin B_1 deficiency are not caused by any toxic effect of accumulated lactate, or any other metabolite, [8, 54] but a "biochemical lesion" brought about by the "absence of an important factor in the development of energy from carbohydrate." The inability of the cardiac muscle and the central nervous system to obtain energy from normal processes of carbohydrate metabolism in which vitamin B_1 plays a role appears to be more significant than the by-products of such failure.

In considering the mechanism of production of the abnormal T waves which are observed in vitamin B_1 deficiency, it is of interest to note the effects of monoiodoacetic acid.[55] Nahum and Hoff[56] observed in the electrocardiograms of the cat an inversion of the T waves after giving

monoiodoacetic acid, which blocks glycolysis and prevents the accumulation of lactic acid. No change was observed, however, after giving sodium cyanide, which promotes such an accumulation. From this they conclude that changes in the S-T segment in their experiments were related, not to the presence of metabolites or to failure of oxidation, but to a loss of the anaerobic energy of glycogen breakdown. Peters and O'Brien[57] have shown that the oxidation of pyruvate which takes place in the pigeon's brain in the presence of vitamin B_1 is inhibited by iodoacetate. These observations suggest that the electrocardiographic changes which we have observed in the rat heart in vitamin B_1 deficiency, which are similar to the changes after administering monoiodoacetic acid, may be brought about by the same mechanism as that suggested by Nahum and Hoff. This is further confirmed by the recent observation that, although the oxygen consumption of the auricles of deficient rats is reduced, there is no significant difference in the oxygen consumption of the ventricular tissue of normal and deficient rats.[58]

SUMMARY AND CONCLUSIONS

1. In order to ascertain whether the cardiac manifestations of vitamin B_1 deficiency could be induced by the presence of intermediary metabolites, electrocardiograms were recorded on rats before and after single and repeated doses of sodium pyruvate, pyruvic acid, sodium lactate, lactic acid, sodium bicarbonate, ammonium chloride, methyl glyoxal, glyceraldehyde, glucose, and sodium adenylate, administered by various routes.

2. The *fatal doses* of sodium pyruvate, but not of pyruvic acid, sodium lactate, lactic acid, methyl glyoxal, or glyceraldehyde, were lower for deficient than for normal rats.

3. In normal rats the heart rate and T waves usually remained unchanged after *single, nonfatal doses* of pyruvate, pyruvic acid, lactate, lactic acid, methyl glyoxal, or glyceraldehyde, when they were administered orally or subcutaneously. The heart rate often decreased after intravenous injection of pyruvate, lactate, or glyceraldehyde. In rats deficient in vitamin B_1, the heart rate often decreased after subcutaneous injection of pyruvate or lactate, or after intravenous administration of methyl glyoxal. In deficient rats the height of the T waves regularly increased after subcutaneous or intravenous administration of sodium pyruvate. In several animals the T waves were also higher after the injection of lactate or sodium bicarbonate. In both normal and deficient rats, sodium adenylate caused no symptoms except a prompt and marked decrease in the heart rate, which was not abolished by atropine. In the majority of cases the P-R interval did not show any definite alteration after the administra-

tion of any of the substances used. Neurologic symptoms corresponding to those in vitamin B_1 deficiency were not observed after nonfatal doses of the metabolites studied.

4. In about one-third of the normal rats, *repeated daily doses* of pyruvate, pyruvic acid, lactate, lactic acid, methyl glyoxal, or glyceraldehyde brought about a slight decrease in the level of the heart rate. The T waves were unchanged, and no neurologic symptoms were induced. In deficient rats which were receiving repeated doses of the same substances, the weight and heart rate usually increased normally after thiamin was given. After administering pyruvate, however, the cardiac response to thiamin was sometimes delayed in deficient rats. In three instances, methyl glyoxal or glyceraldehyde probably lengthened the period during which rats could be maintained on a given dose of thiamin.

5. Large doses of thiamin (0.09 to 2.32 mg. per 100 grams of body weight, corresponding to 60 to 1,600 mg. in a man of 70 kilograms) had little, if any, effect on the heart rate and electrocardiographic complexes of normal rats and dogs, and produced no toxic responses. A vagotonic effect of thiamin on the dog heart could not be definitely established.

6. A few rats which were deficient in riboflavin, vitamin B_6, or vitamin A did not show the T-wave and heart rate changes observed in vitamin B_1 deficiency.

7. The experiments presented indicate that rats deficient in vitamin B_1 were somewhat more sensitive than normal animals to large doses of pyruvate. Because of the size of the doses and the magnitude of the changes, however, no physiologic significance can be attached to the findings. The results of this study indicate that the accumulation of metabolites is probably not an important causal factor in the production of cardiac manifestations in vitamin B_1 deficiency in rats, and support the theory that these manifestations depend on a defect in metabolism, rather than on a toxic effect of circulating metabolites.

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A STUDY OF THE EFFECTS OF NICOTINIC ACID AND RELATED PYRIDINE AND PYRAZINE COMPOUNDS ON THE TEMPERATURE OF THE SKIN OF HUMAN BEINGS

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INTRODUCTION

WHEN it was first reported that nicotinic acid and its amide were of specific value in treating canine blacktongue,[1] there was no information regarding the pharmacologic activity of these pyridine compounds in man. Before these substances could be used in the treatment of pellagra, it was necessary to ascertain whether they were toxic for human beings. Preliminary observations by Spies, Cooper, and Blankenhorn[2] indicated that nicotinic acid could be given safely to normal adults, either orally or parenterally. It was found, however, that when this substance was given orally in large amounts, or was administered rapidly by the parenteral route, a sensation of heat, itching, and tingling, together with flushing of the skin, frequently occurred. This fact, which was noted independently by several investigators,[2] was surprising, for no similar observations had been made on dogs or other experimental animals.[3-6]

Nicotinic acid, when administered orally or parenterally in sufficient doses, produces a characteristic train of symptoms. Within from five to ten minutes after an oral dose of 100 mg., or more, or one or more minutes after the parenteral administration of 10 mg., a sensation of heat occurs in the skin. It usually begins in the face and spreads over the neck, chest, and upper arms. In some cases, the entire body surface becomes involved, although the arms and legs frequently escape, and the surface temperature may actually fall, especially in the lower extremities. The sensation of heat may merge into, or be complicated by, stinging, itching, and tingling of the skin. Occasionally, actual pain is experienced. Simultaneously with this feeling of heat, there is a diffuse flushing of the areas in which the heat is felt. Usually the sensation of heat diminishes before the color returns to normal, and the skin temperature may remain elevated even when the skin feels normal subjectively. These phenomena of vasodilatation are associated with a measurable rise in skin temperature, so that we have available an

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objective gauge of the degree of change occurring in the vessels of the skin. The curve of temperature change may vary from one person to another, but each person repeatedly reacts according to his own pattern. Using rigorously controlled standard conditions in a single subject, it is possible to test drugs of the pyridine series for the presence or absence of vasodilating power. The present paper deals with such a study.

MATERIAL AND METHODS

The subjects of these studies included forty-seven adult men, seven women, and four children. None of them showed evidence of peripheral vascular disease or of local skin lesions. Each test was made when the subject was in the post-absorptive state, i.e., usually after fasting from suppertime until the afternoon of the following day (about twenty hours). Occasionally, subjects fasted only during the period from after breakfast until early afternoon (six hours). For at least one hour, and usually for two hours, before the test, the subject was kept flat in bed in a constant-temperature room (20° C.). Under these conditions, the degree of vasoconstriction became so well stabilized that there was no temperature fluctuation of more than ± 0.3° C. in the region tested for the duration of these tests. In our early studies, all of the subject's clothing was removed, and skin temperature readings were made on the legs, arms, chest, neck, and face. After a few trials, it was found that the most extensive responses to the vasodilators occurred in the face and neck, a point recently stressed by Kunkel, Stead, and Weiss.[7] The data included in this paper are derived from repeated readings of the skin temperature of many areas of the face and neck only.

The temperature measuring unit employed in these studies was the Taylor "Dermatherm,"* which consists of four sensitive thermocouples connected in series to form a thermopile; the terminals are connected to a special millivoltmeter which is calibrated to read in degrees centigrade.[8] Before each series of readings, the thermopile was held on the skin in an area not to be studied, until it was of approximately the same temperature as the skin. Precautions were taken not to press on the skin too hard, as this may alter the circulation in the subjacent region.[9] Before each observation was recorded, the thermopile was held (from four to seven seconds) against the part to be studied, until the oscillation of the recording needle of the millivoltmeter ceased. The time required for completing the fifteen readings was usually two minutes. The time recorded on the charts is that at which the observations were begun.

Fig. 1 shows the fifteen areas on the face and neck where temperature was recorded repeatedly at regular intervals, varying from five to fifteen minutes. After a base line had been established, i.e., when there was no spontaneous temperature change in two or more observations, the substance to be tested was given either orally or intravenously. Skin temperature readings were recorded at regular intervals, until the maximum change was detected and a return toward normal had occurred, or for a sufficiently long period to be sure that no change would appear. Control readings were made a day or two before or after the test, under identical conditions. Whenever a compound was tried for the first time, it was given in much smaller doses and more slowly, and records of skin temperature were not always made.

Since some of the compounds were available in only small amounts, all of the data used in making the charts (Figs. 3, 5, and 7) represent the effect of giving 20 mg. of the test substance intravenously. Each curve in Figs. 3, 5, and 7 is an

*The authors are indebted to Dr. Louis G. Herrmann for his kindness in placing the constant-temperature room and apparatus of the vascular clinic at their disposal, and to Miss Helen Crisenberry for her help in recording the temperature readings.

average of observations on four subjects. In no case was there a considerable variation from the average. The substances studied were: nicotinic acid; its sodium, ammonium, ethyl, and monoethanolamine salts; quinolinic, dinicotinic, 2,6-dimethyl dinicotinic, 6-methyl nicotinic, and isonicotinic acids; nicotinic acid amide; nicotinamide hydrochloride; nicotinic acid N-diethyl amide (coramine); pyridine; 3-amino pyridine; sodium sulfapyridine; vitamin B_6 (2-methyl, 3-hydroxy, 4,5-di-[hydroxymethyl] pyridine); and pyrazine mono- or 2,3-dicarboxylic acids.* The material was dissolved in 20 c.c. of physiologic salt solution or sterile water. The injection was completed within one to three minutes. No untoward reaction occurred with any of the compounds used in this study when they were given in this way.

In an earlier paper, Spies, Bean, and Stone[10] noted a considerable variation after oral administration under the same conditions. Examining only the face and neck, and with other factors rigidly controlled, we later found that the temperature rise in any given case followed a definite pattern when the doses were identical and were administered by the same route. We have repeated intravenous injections and obtained identical responses in one case twice on the same day. The flushing response may be elicited again within an hour after a first reaction when small doses are given parenterally. Although a number of factors, such as intestinal absorption, degree of saturation with nicotinic acid, and rate of excretion, undoubtedly influence the occurrence and severity of the reaction after oral administration to normal persons and pellagrins, these factors made no difference when doses of 20 mg. were given intravenously.

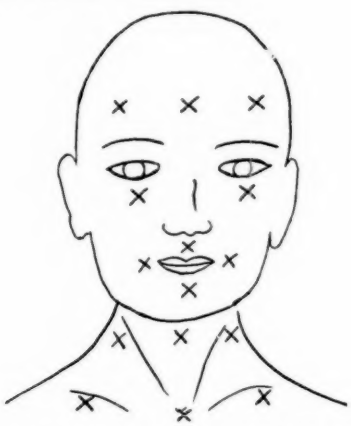


Fig. 1.—Crosses indicate areas on the face and neck where temperature readings were made.

I. PYRIDINE COMPOUNDS WHICH INDUCE THE VASODILATOR RESPONSE

Preliminary reports of the work to be described were made by Spies, Cooper, and Blankenhorn,[2] who noted a reaction characterized by "severe flushing, itching, and tingling, particularly of the face and extremities, which occurred within twenty minutes after the administration of nicotinic acid." Spies, Bean, and Stone[10] more specifically stated that "the giving of nicotinic acid in oral doses of 200 mg., or in intravenous doses of 10 mg. within one minute, nearly always produces dilatation of the small vessels of the face and upper part of the trunk.

*We are indebted to the S. M. A. Corporation, Abbott Laboratories, Merck and Company, and Mead Johnson and Company for the various compounds used in these studies.

This is characterized by increased temperature, flushing, burning, and itching sensations. The pulse, blood pressure, respirations, and electrocardiogram are not regularly changed."

There was, then, evidence that nicotinic acid produced a vasodilatation in the skin, which was attended by little or no general relaxation of the larger arteries throughout the body. According to the method outlined above, compounds structurally related to nicotinic acid were tested. It was found that identical responses were produced by nicotinic acid (3-pyridine carboxylic acid), sodium nicotinate, ammonium nicotinate,

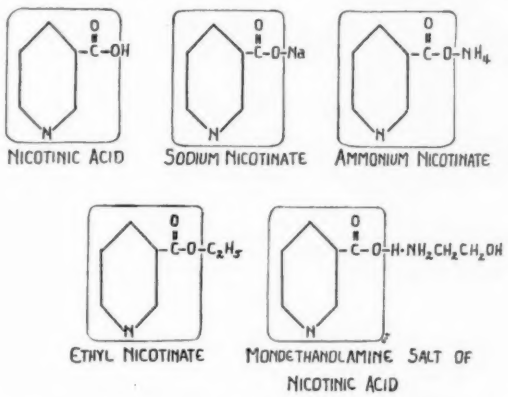


Fig. 2.—Formulas for pyridine compounds which produce temperature rise in the skin. The specific radical involved is enclosed in the box.

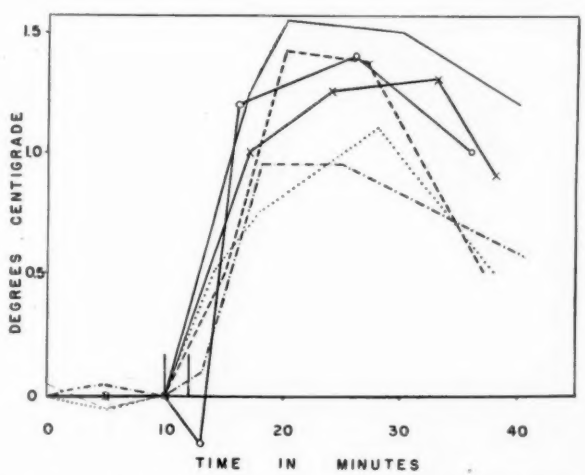
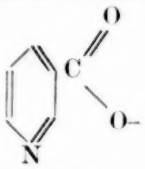


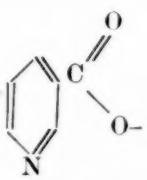
Fig. 3.—Variation in facial temperature after the administration of pyridine compounds. The short vertical lines indicate the period during which the drug was injected. Each record (in Figs. 3, 5, and 7) is an average of tests on four subjects, except for ethyl nicotinate, which was used on only two subjects.

Nicotinic acid
Sodium nicotinate
Ammonium nicotinate
Ethyl nicotinate
Monoethanolamine salt of nicotinic acid
Irradiated nicotinic acid

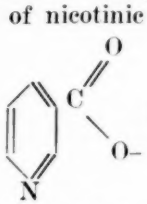
ethyl nicotinate, and the monoethanolamine salt of nicotinic acid (Figs. 2 and 3).* Furthermore, it was found that irradiating nicotinic acid for several hours did not abolish the vasodilator potency of samples from several different sources.† Examination of the structural formulas of these several pyridine compounds reveals that they have in common one

radical, namely,  with some atom attached to the unsaturated oxygen atom (Fig. 2). It is believed that the quantitative difference in degree or duration of vasodilatation illustrated in Fig. 1 is an expression of individual differences among subjects. In one subject on whom all of the above drugs were tried, the curves of temperature rise were identical with respect to extent of rise, time of maximum change, and length of time before returning to the base line. There was no essential difference in the reaction produced by any of these compounds.

II. PYRIDINE COMPOUNDS WHICH DO NOT INDUCE THE VASODILATOR RESPONSE

(a.) *Pyridine Compounds Containing the*  *Radical.*—

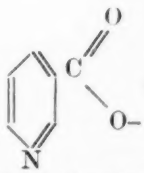
Similar tests were done with a number of compounds containing the radical which was found to be associated with the flushing reaction, but containing, in addition, other radicals substituted in one or more positions. Dinicotinic acid, 2,6-dimethyl dinicotinic acid, and quinolinic acid produced no flushing or increase in skin temperature (Figs. 4 and 5). In addition to the intravenous administration, large doses (200 to 500 mg.) of these compounds were given orally, with no subjective or objective changes. A dose of 50 mg. of 6-methyl nicotinic acid was given intravenously to one subject, and no increase in temperature occurred, although he reacted readily to 20 mg. of nicotinic acid. The

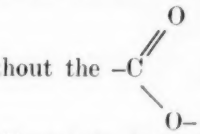
addition of other radicals to the pyridine ring  in the 2, 5,

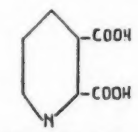
or 6 position, or in all three, caused a loss of the vasodilating property.

*Ferrous nicotinate and quinine nicotinate have been studied recently. Both showed pronounced vasodilator potency, but quinine nicotinate produced extreme tinnitus when given intravenously.

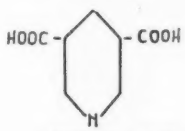
†We are indebted to Dr. C. E. Bills, Research Laboratory, Mead Johnson and Company, Evansville, Ind., for some of these samples, and to Dr. S. P. Vilter, Department of Biochemistry, University of Cincinnati College of Medicine, for others.

(b.) *Pyridine Compounds Not Containing the*  *Radical.*—

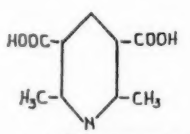
The same procedure was followed with a number of chemicals containing the pyridine ring, but without the  in the 3 position. No increase in skin temperature followed the injection of pyridine, 3-amino pyridine, sodium sulfapyridine, nicotinamide hydrochloride, isonicotinic



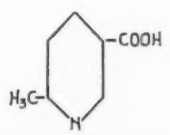
QUINOLINIC ACID



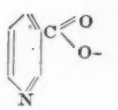
DINICOTINIC ACID



2-6 DIMETHYLDINICOTINIC ACID



6 METHYL NICOTINIC ACID

Fig. 1.—Pyridine compounds containing the  radical, but without vasodilator potency.

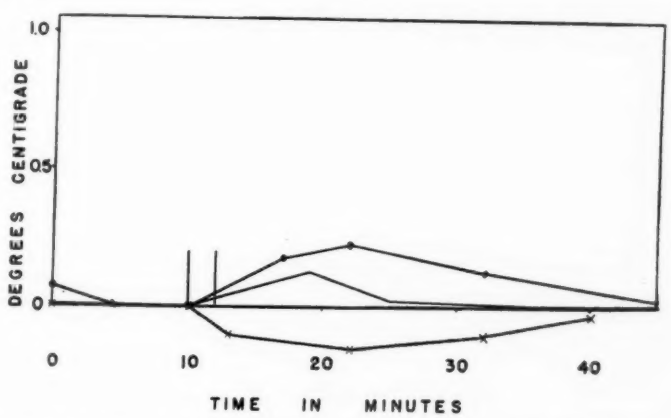


Fig. 5.—Variation in facial temperature after administration of pyridine compounds: Dinicotinic acid, ——x——x——x——; quinolinic acid, ——.——.——.——; 2, 6-dimethyl dinicotinic acid, ————————. The variations are not considered significant.

acid, nicotinic acid amide, or coramine (nicotinic acid N-diethyl amide) (Figs. 6 and 7). This indicates that pyridine, sulfapyridine, and amino pyridine are not skin vasodilators. Of more interest is the fact that no increase in skin temperature was produced by nicotinic acid amide or nicotinic acid N-diethyl amide. These compounds differ from those producing the temperature rise only in that another radical is substituted for one of the oxygen atoms in the $-C\begin{matrix}=O\\-O-\end{matrix}$ group. Vitamin B_6

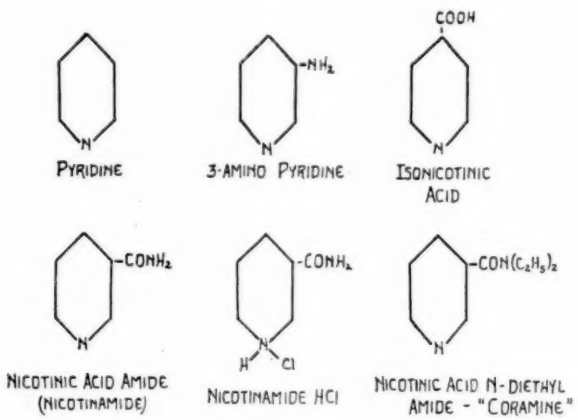
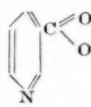


Fig. 6.—Pyridine compounds not containing the  molecule, and without vasodilator potency.

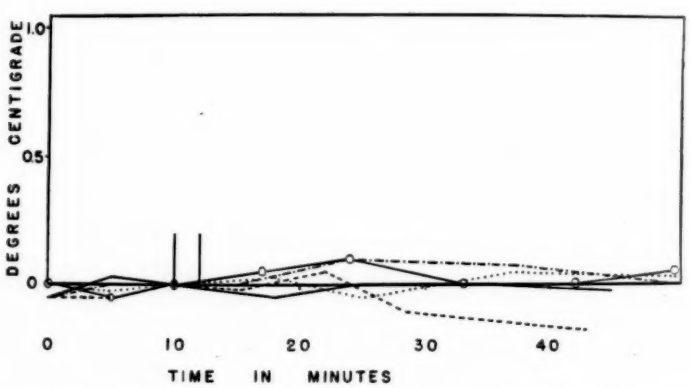


Fig. 7.—Variation in facial temperature after administration of pyridine compounds.

Pyridine . . . . . .
β-amino pyridine ———————
Coramine ——o——o——o——o
Nicotinamide - - - - - - - -
Nicotinamide HCl -·-·-·-·-·-·-·-

(2-methyl, 3-hydroxy, 4, 5-di-[hydroxymethyl] pyridine) has recently been studied in the same way, and in four normal subjects it was found that there was no temperature response to the injection of 50 mg. intravenously. All subjects tested with the substances which did not evoke the increase in skin temperature were found to respond to nicotinic acid with an increase in skin temperature.

(c.) *Pyrazine Compounds.*—Because there is evidence that both the mono- and 2,3-dicarboxylic acids of pyrazine (Fig. 8) are effective in treating pellagra,[15] we have tested these substances in the same way as the pyridine compounds. In four subjects there was no elevation of skin temperature or any subjective change after the intravenous injection of from 20 to 50 mg. The curves in these cases were flat, as are those in Figs. 3 and 5 and in the control tests.

Subsequently, in a study of the effect of several additional batches of pyrazine monocarboxylic acid on ten subjects, three were observed to flush, and they had a rise of temperature of 0.5° C. These same subjects responded to similar doses of nicotinic acid with a temperature increase of from 1.5 to 2.0° C.

PYRAZINE 2-3 DICARBOXYLIC ACID

PYRAZINE MONOCARBOXYLIC ACID

Fig. 8.—Pyrazine compounds without regular vasodilator potency.

III. ABSORPTION

A comparison of the time which elapsed between the administration of nicotinic acid by intravenous and oral routes and the flushing reaction is presented in Fig. 9. It indicates that the response to intravenous administration began rapidly, reached a peak in about ten minutes, and disappeared rather rapidly. Usually, the temperature had returned to the base line within from thirty to forty-five minutes. The same figure shows that, when 200 mg. were given orally (ten times the intravenous dose in this test) to the same individual, under identical conditions, the temperature rose more gradually, reached the same peak, and then subsided much more slowly. The initial sensations, after intravenous medication is begun, frequently occur during the first minute, while the solution is still being injected, but the end point is not sharp. However, there may be no objective or subjective change for from fifteen to thirty minutes after oral administration.

Another interesting fact in regard to absorption is shown in Fig. 10, in which a comparison of the temperature rise in the fasting and post-

prandial states is made. When 500 mg. were given to the fasting subject, there was a definite rise in fifteen minutes. When the same amount was given after a meal, this rise did not appear for twenty-two minutes. In addition, the peak was 0.7° C. lower than when the material was taken on an empty stomach. Such observations have repeatedly verified the clinical impression[2, 4] that the flushing and burning are less severe when the drug is given orally after meals.

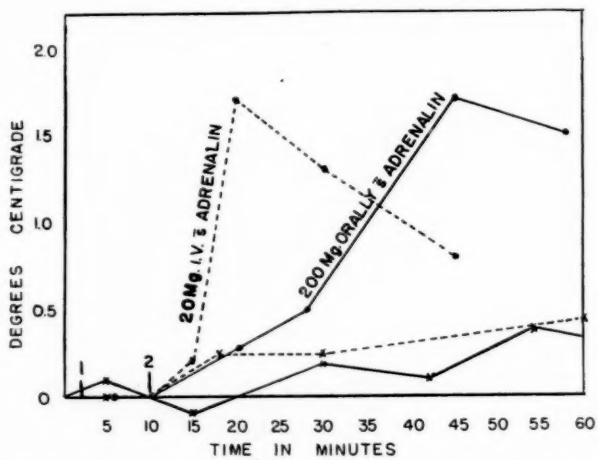


Fig. 9.—A comparison of the temperature response after the oral and intravenous administration of nicotinic acid, with and without previous injection of 1 c.c. of adrenalin. *1*, Time at which 1 c.c. of adrenalin was given intravenously; *2*, time at which 20 mg. of nicotinic acid were given intravenously.

Nicotinic acid intravenously, no previous adrenalin ----·----·----·
Nicotinic acid intravenously, after 1 c.c. of adrenalin ----x----x----x
Nicotinic acid orally, no previous adrenalin ——·——·——·
Nicotinic acid orally, after 1 c.c. of adrenalin ——x——x——x

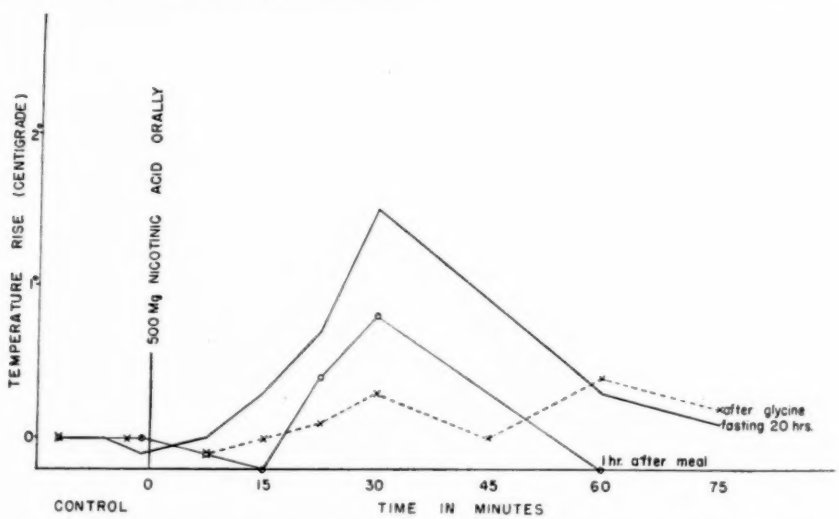


Fig. 10.—A comparison of temperature response to 500 mg. of nicotinic acid, administered orally to a subject in a fasting condition, just after a meal, and after ingestion of 30 Gm. of glycine during the preceding one-half hour.

IV. GLYCINE (AMINOACETIC ACID)

As has been previously reported,[10] we have found that when glycine is given orally in from 30 to 60 Gm. amounts during the one-half-hour period before nicotinic acid is given orally, the vascular response is decreased, or, in many cases, even abolished (Fig. 11). When the same amount of glycine is given orally and nicotinic acid is given by vein (in doses of from 10 to 20 mg.), the flushing response occurs just as it does without glycine.

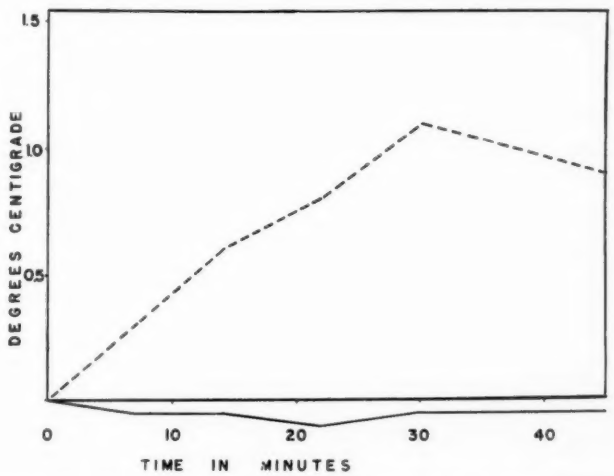


Fig. 11.—A composite graph showing the difference in skin temperature response in ten normal subjec s following ingestion of 200 mg. of nicotinic acid after 60 Gm. of glycine were taken orally during the one-half hour before the test (lower line), and without glycine (broken line). In two cases there was a rise of 0.5° C. after glycine, but this was only one-third the rise when no glycine was given in a control test.

V. SITE OF ACTION

While these studies suggest that a specific radical is essential in producing the temperature rise, they give no indication of the nature of the response. Special studies with adrenalin throw some light on the probable site of the reaction. Fig. 9 shows that when 1 c.c. of adrenalin was given intravenously eight minutes before the administration of nicotinic acid, the vasodilatation was much less than that which took place when no adrenalin was given. In the experiments recorded in Fig. 9, there was no flushing of the face after adrenalin had been given, but there was slight flushing of the neck (with some concomitant rise in surface temperature). A number of studies were carried out in which adrenalin was given after the oral or parenteral administration of nicotinic acid, and it was found that the temperature returned to the base line more rapidly than in control experiments. When adrenalin was injected subcutaneously and allowed to permeate a small area in the skin, this region stood out as a blanched spot in the flushed skin when nicotinic acid, in doses adequate to produce flushing, was

given subsequently. The dosage and timing could be so arranged as to produce no change or only a slight flushing. When very large doses of nicotinic acid and small injections of adrenalin were given, the vasodilator effect would break through, or the adrenalin effect would wear off and the skin become warm. Thus, it is clear that there is an antagonism between adrenalin and nicotinic acid, in so far as the arterioles of the vasolabile regions of the skin are concerned. By inference, we conclude that nicotinic acid acts, directly or indirectly, upon the arterioles in the skin.

We have not been able to obtain any evidence that nicotinic acid exerts a similar effect upon arterioles throughout the entire body, although the evidence to the contrary is not conclusive. We have been able to find no constant and reproducible changes in the electrocardiogram, arterial blood pressure, or pulse rate during the period of flushing. Observations of the mucous membranes in various parts of the body (mouth, nose, rectum, vagina) have not revealed any vascular response during the reaction in the skin. No changes in the retinal vessels could be detected by means of the ophthalmoscope during the dermal reaction. All of these observations lend support to the supposition that the vasodilator action is most active in the skin arterioles.

VI. TOXIC ACTION

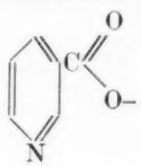
We have administered nicotinic acid, or one of the closely related pyridine derivatives, to more than one thousand persons, and have taken it ourselves, with no apparent toxic effect. We have given single doses of 1.5 Gm. orally, 50 mg. intravenously within three minutes, and 75 mg. intramuscularly, to adults, without ill effects, although the flushing lasted longer than with smaller doses. We do not recommend such heroic doses for therapeutic purposes, for it is more pleasant to take repeated small doses, and, in most cases, it is theoretically more sound to give the drug slowly than to flood the organism with a massive amount at one time. In addition to the flushing reaction, which all observers have found in cases in which adequate doses of nicotinic acid were given, a few toxic reactions have been reported. Those who have used the drug extensively have observed an occasional case in which nausea, epigastric distress, or even vomiting has occurred.[10, 11, 14, 15] Throbbing of the head and dizziness have been noted. Rachmilewitz and Glueck[12] observed a case of an "urticarial rash" which lasted for two hours, and Manson-Bahr and Ransford[13] reported that an "urticarial rash appeared on the chest, arms, and front of the thighs. No treatment was given, and within half an hour all symptoms and signs of drug intoxication had disappeared." Alport, Ghalioungui, and Hanna[14] recorded a case in which severe epigastric pain and colic followed each dose of 1 Gm. of nicotinic acid. These all occurred in patients with pellagra. Ruffin and Smith[15] observed lassitude and mental depression, palpitation, cyanosis, substernal oppression, headache, nausea, dyspnea,

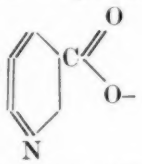
and vomiting, in addition to the flushing, in several of ten normal adults to whom they gave 250 mg. orally four times a day for several days. These symptoms were so disagreeable that many of their subjects discontinued the experiment.

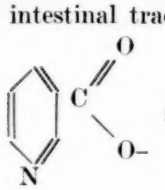
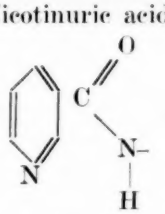
VII. COMPARISON OF THE EFFECTS OF NICOTINIC ACID AND HISTAMINE

In certain respects, the reaction caused by nicotinic acid resembles that produced by histamine. It does not lose its vasodilator effect when it passes through the capillaries.[4] The skin reaction produced by nicotinic acid resembles in color and temperature change that effected by histamine. The effect of intracutaneous injection is very much weaker than that produced by histamine. If, before nicotinic acid is given, an area in the skin is subjected to mild trauma, such as tight application of a tourniquet or brisk rubbing, this region becomes more flushed than adjacent areas, its temperature rises higher than that of a symmetrically situated area, and the subjective symptoms are more intense. Localized edema may appear in such an area. It has been found that when nicotinic acid is given intravenously in quantities adequate to cause flushing, there is usually an increase in the secretion of gastric hydrochloric acid.[10] We have not observed this effect with doses inadequate to cause flushing. In this connection, the observations of Kalk[16] are of interest. He found that, in certain susceptible persons, irritation of the skin was followed by an increase in gastric secretion comparable to that produced by administering histamine, presumably through the liberation of histamine. These observations suggest that, since nicotinic acid, when injected or taken by mouth, has certain actions similar to histamine, it may function through the liberation of histamine in the tissues. It is also entirely possible that the vascular and gastric reactions are not mediated through the liberation of histamine, but are a peculiar effect of nicotinic acid and some of its salts on certain groups of blood vessels. Studies with histaminase are now being made in the hope of settling this question.

DISCUSSION

The foregoing observations indicate that the vasodilator effect of the pyridine compounds which were studied is a highly specific action of only such of them as contain the  structure. All compounds in which one of the ring hydrogens had been substituted, or in which an addition had been made to the ring nitrogen, were inactive. The aminization of the carboxyl group in nicotinic acid (nicotinamide) rendered it inert, as did complete removal (pyridine). The pyrazine

derivatives which were studied rarely caused vasodilatation. The vasodilator activity of these pyridine compounds appears to be a specific property which resides only in those which contain the  structure, free from any substituted or added radicals, except at the unsaturated oxygen atom.

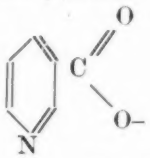
Since satisfactory results have been obtained in treating pellagra with coramine,[10] nicotinamide,[2, 14] and other drugs,[17] it is obvious that the molecule which has a beneficial effect in the treatment of pellagra is not necessarily the same as that which produces the vascular reaction. Of the pyridine compounds which we studied, all that produced the changes in the skin vessels are of value in treating pellagra. On the other hand, some of the compounds which do not cause the vascular reaction are potent remedies for pellagra. It is possible, therefore, to get a therapeutic response without the unpleasant flushing. It is also possible, nonetheless, to give nicotinic acid in repeated small doses, so that the skin changes do not occur, in which case it is just as effective. The skin temperature changes produced by nicotinic acid were found to be delayed or aborted by the ingestion of ordinary food just prior to taking the drug. Glycine, by mouth, checks the vasodilatation produced by nicotinic acid. It is possible that glycine interferes with, or inhibits, the absorption of unchanged nicotinic acid, which is therefore not present in a concentration sufficient to arouse the response. It might be crowded out in some such fashion as it is when given after meals during normal digestion. We believe that it is more probable, however, that glycine and nicotinic acid combine to form nicotinuric acid,[1] either in the intestinal tract or in the liver. Nicotinuric acid does not contain the  group; the linkage is  , which we have found does not have any observable effect upon the vessels.

It is inferred from studies with adrenalin that the vasodilatation takes place in the arterioles of the skin. Flushing, itching and heat in the skin, and increased motility of the stomach and secretion of gastric HCl are changes similar to those produced by histamine, and it is possible that histamine is liberated by nicotinic acid.

The discovery of a skin vasodilator as innocuous, effective, and cheap as nicotinic acid naturally has suggested many uses for it, in addition to its utility as a vitamin. It has been applied to a great number of skin diseases and may perhaps be of value merely for its local circulatory

effects. The use of nicotinic acid in the treatment of peripheral vascular disease should be discouraged, for, in some cases, it seems to decrease blood flow in the limbs.[10]

SUMMARY AND CONCLUSIONS

1. Of the pyridine compounds which we studied, all which contained the free  radical produced vasodilatation of the skin and an increase in skin temperature in normal human beings, when given intravenously in doses of 20 mg. These compounds were nicotinic acid and its sodium, ammonium, ethyl, and monoethanolamine salts. Pyrazine monocarboxylic acid produced a slight rise of temperature in a few cases. These compounds are all effective in treating pellagra.

2. No vasodilatation followed the administration of similar amounts of quinolinic acid, nicotinic acid amide, nicotinic acid N-diethyl amide, and pyrazine 2,3-dicarboxylic acids, which are effective antipellagric compounds. No vasodilatation followed the injection of similar doses of dinicotinic acid and 2,6-dimethyl dinicotinic acids, which have some antipellagric value.

3. No vasodilatation was produced by 6-methyl nicotinic acid, nicotinamide hydrochloride, and isonicotinic acid. These compounds have not been tested sufficiently for antipellagric potency.

4. No vasodilatation followed the injection of 20 mg. of pyridine, beta-amino pyridine, sodium sulfapyridine, and vitamin B_6 (2-methyl, 3-hydroxy, 4,5-di-[hydroxymethyl] pyridine), which have no specific value in treating pellagra.

5. The use of nicotinic acid in the treatment of peripheral vascular disease should be discouraged, for, in some cases, it seems to decrease blood flow to the extremities, particularly the legs.

6. The site and possible mechanism of the vasodilator action have been discussed.

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A COMPARISON OF THE ORTHODIAGRAM WITH THE TELEOROENTGENOGRAM

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IN A RECENT study of 133 cases in which orthodiagrams and teleoroentgenograms taken at seventy-eight inches were made consecutively, we were impressed by certain marked differences in the heart and chest measurements which were obtained by the two methods of examination. That the cardiac silhouette is magnified in teleoroentgenograms is well known.[1, 2, 3, 4] The magnification of flat objects which occurs in teleoroentgenography can be computed by a simple algebraic equation; the variables are the object-film distance and the target-film distance. The enlargement, however, may be increased by improper centering. Although the fact that the heart shadow is magnified in teleoroentgenograms is well known, the degree of enlargement is not generally appreciated. Furthermore, it is not generally known that the magnification is unequal for the various portions of the heart, and, as a result, that the silhouette is distorted.

A comparison of orthodiagrams and teleoroentgenograms cannot be made with mathematical accuracy because (1) it is impossible to be certain that the chest is in exactly the same position in relation to the film and fluoroscopic screen, (2) it is most difficult to obtain teleoroentgenograms and orthodiagrams in the same phase and degree of respiration (the possibility of error is increased if the teleoroentgenograms and orthodiagrams are not made consecutively), and (3) it is difficult to obtain both in the same phase of the cardiac cycle.

In this study efforts were made to minimize all possible sources of error. The two studies were done consecutively, at the end of an ordinary inspiration, and orthodiagrams were drawn in diastole in order to obtain the largest heart size. Possible errors incident to orthodiagraphy, such as might arise by the use of a large beam of light and movements of the heart during respiration, were well appreciated and avoided.

In order to compare the two methods of examination more accurately, a model of the heart was used. The above-mentioned factors which make impossible an accurate comparison of orthodiagrams and teleoroentgenograms in the living were, therefore, eliminated. Furthermore, the dimensions of the model can be easily ascertained, so that the two methods of roentgenologic examination of the heart can be compared not only with each other, but with actual measurements.

The roentgenographic apparatus used was so arranged that the casette holder and fluoroscopic screen were in different tracks, and could be interchanged by lowering or raising one or the other; the centers of both were in the same vertical

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line. Because of this construction, the film was approximately one inch from the anterior surface of the chest. The necessary correction was made in measuring target-film and object-film distance. The model, made immovable in a box, was placed upon a table, and the center of the anterior surface was made to correspond with that of the fluoroscopic screen. The centers of the screen (and casette), of the model, and of the x-ray tube, at a distance of 6½ feet, were in one line. An orthodiagram was made with the model as close to the screen as possible, and immediately thereafter a film was exposed without moving the model. This procedure was repeated at a distance of zero to six inches, inclusive (actually one to seven inches).

Table I shows the various measurements of the model and those of the orthodiagram and teleoroentgenogram, taken at various distances.

TABLE I

OBJECT-FILM DISTANCE	TRANSVERSE DIAMETER OF HEART (CM.)					AORTA VAQUEZ-BORDET (CM.)				
	ACTUAL MEASUREMENT	ORTH.	PER CENT DIFFERENCE	ROENTGENOGRAM	PER CENT DIFFERENCE	ACTUAL DIAMETER	ORTH.	PER CENT DIFFERENCE	ROENTGENOGRAM	PER CENT DIFFERENCE
1 inch	12.5	12.6	0.8	13.0	4.0	9.2	9.1	-1.1	9.9	7.6
2 inches	12.5	12.6	0.8	13.2	5.6	9.2	9.2	0	10.0	8.7
3 inches	12.5	12.6	0.8	13.3	6.4	9.2	9.0	-2.2	10.1	9.8
4 inches	12.5	12.7	1.6	13.5	8.0	9.2	9.0	-2.2	10.2	10.9
5 inches	12.5	12.5	0	13.6	8.8	9.2	9.0	-2.2	10.5	14.1
6 inches	12.5	12.5	0	13.8	10.4	9.2	9.2	0	10.5	14.1
7 inches	12.5	12.6	0.8	13.8	10.4	9.2	9.1	-1.1	10.7	16.3

Examination of Table I shows that measurements obtained on roentgenograms are consistently higher than actual measurements and those obtained by orthodiagraphy. As the object-film distance increases, the error becomes considerable, and is greatest for the aorta. Although a distance of six or seven inches from film to anterior surface of the heart is not common clinically, this object-film distance may occur in the case of obese individuals, especially women with pendulous breasts, and also when patients have chest deformities, especially pigeon chest. The anteroposterior diameter of the model was 5.6 cm. (2.2 in.), so that, at an object-film distance of six inches from the anterior surface of the heart, the anterior portion of the aorta was 8.2 inches from the film. This distance, although not common, may occur in cases of emphysema, kyphosis, and also when the subject is obese. The orthodiagraphic measurements were but slightly different from those of the model. Although no changes in transverse diameter were noted at distances of six and seven inches, or in the Vaquez-Bordet diameter at five and six inches, this discrepancy may be accounted for by a slight rotation of the model in relationship to the film.

In the 133 cases, teleoroentgenograms were made immediately after the orthodiagrams. A point slightly to the left of the center of the chest, midway between the most caudal portion of the aorta and lowermost portion of the heart, was marked upon the fluoroscopic screen, and the tube, 6½ feet distant, was centered to this mark. Films were exposed at the end of a normal inspiration.

A comparison of the measurements obtained on orthodiagrams and teleoroentgenograms reveals that, in nearly all cases, the heart and

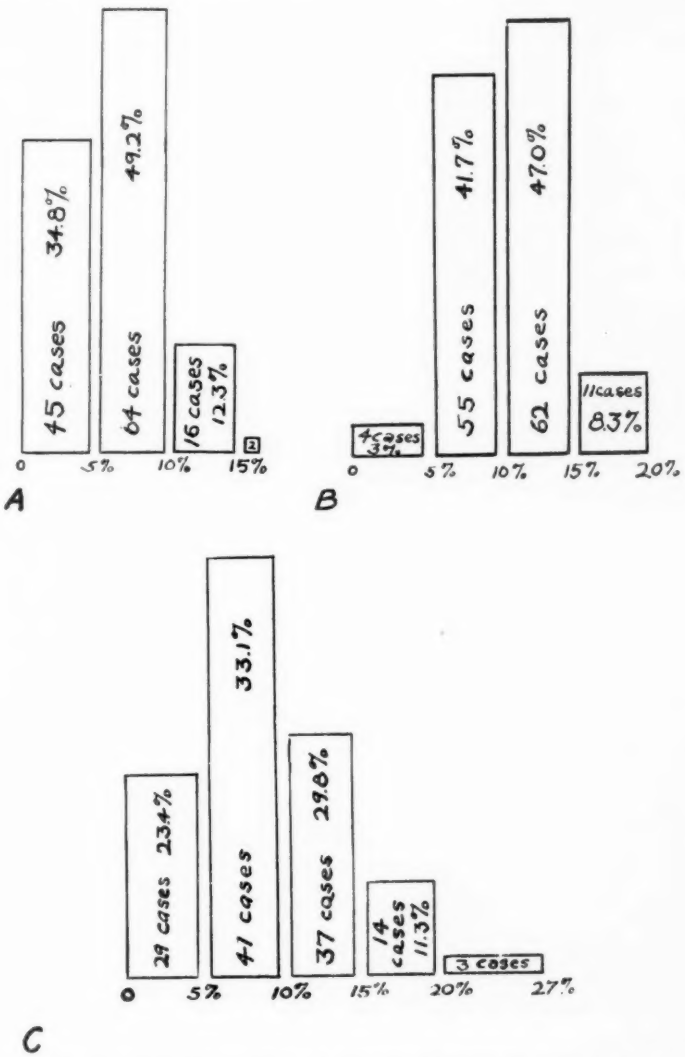

Fig. 1.—*A*, Percentage magnification of transverse diameter of cardiac silhouette in teleoroentgenograms compared with that in orthodiagrams. *B*, Percentage magnification of transverse diameter of chest in teleoroentgenograms compared with that in orthodiagrams. *C*, Percentage magnification of Vaquez-Bordet diameter of aorta in teleoroentgenograms compared with that in orthodiagrams.

chest appear larger in the teleoroentgenograms than in the orthodiagrams. The transverse diameter of the heart was measured satisfactorily in 130 cases, and averaged 6.6 per cent larger in the teleoroentgenogram than in the orthodiagram; the magnification varied from 0 to 16 per cent (Figs. 1*A* and 2). Andrew and Warren,[1] in their study of distortion in roentgenograms, calculated that the magnification of the heart was 6 per cent at a target distance of six feet. In three cases (2.3 per cent), the diameters were equal, in forty-five cases (34.8 per cent) the diameter was 1 per cent to 5 per cent larger; sixty-four diameters (49.2 per cent) were 6 per cent to 10 per cent larger, and eighteen (13.8 per cent) were between 11 per cent and 16 per cent larger. It must be emphasized that the transverse diameter of most hearts is influenced by the height of the diaphragm. The observed difference, therefore, may be inaccurate, because the height of the diaphragm may not have been the same in all cases; in general, however, it is apparent that the transverse diameter of the heart is larger in the teleoroentgenogram than in the orthodiagram. The average variation is approximately that obtained with the model at an object-film distance of three inches.

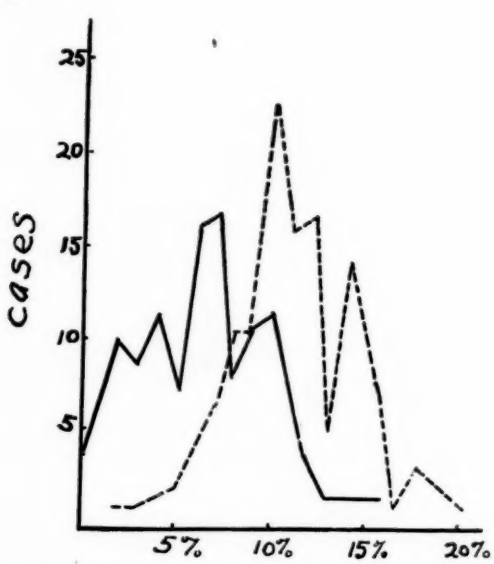

Fig. 2.—Comparison of magnification of transverse diameter of heart (solid line) and chest (dotted line).

The transverse diameter of the chest was measured satisfactorily in 132 cases, and averaged 11.1 per cent higher in the teleoroentgenogram than in the orthodiagram (Figs. 1*B* and 2). As in the case of the cardiac silhouette, an error may arise because of differences in the phase or degree of respiration. Another factor which may be the cause of considerable error, and is frequently not appreciated, is the depth

and shape of the chest. The further the greatest transverse diameter of the chest is from the film, the greater the magnification; if the chest is irregular, the magnification will be unequal (Fig. 3). This factor may be responsible for the greater percentage increase in the transverse diameter of the chest as compared with that of the heart.

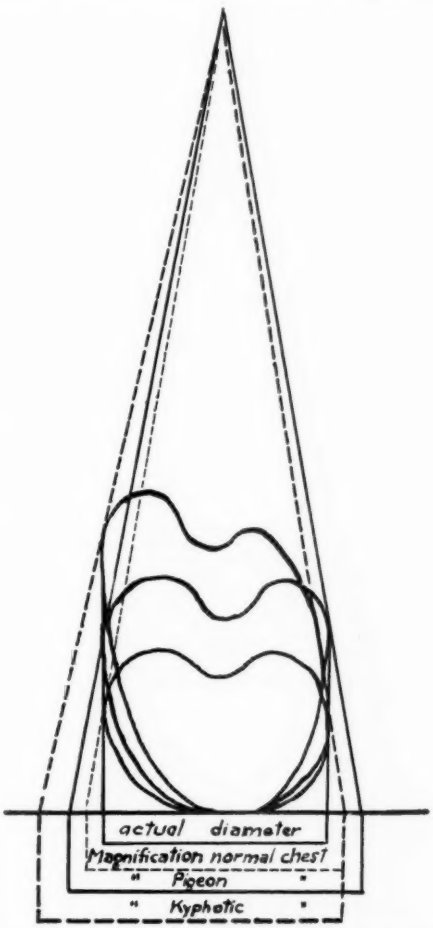

Fig. 3.—Effect of shape of chest upon distortion and magnification.

In four (3 per cent) cases, the transverse diameter of the chest in the teleoroentgenogram was 2 per cent to 5 per cent greater than in the orthodiagram, in fifty-five cases (41.7 per cent), 6 per cent to 10 per cent larger, in sixty-two cases (47 per cent), 11 per cent to 15 per cent larger, and in eleven cases (8.3 per cent), 16 per cent to 20 per cent larger. In 118 cases, the enlargement varied from 7 per cent to 16 per cent.

Inasmuch as the percentage increase in the transverse diameter of the chest is greater than that of the heart in teleoroentgenograms, it follows

that the cardiothoracic ratio should be less in teleoroentgenograms than in orthodiagrams. This was computed in 129 cases. The cardiothoracic ratio was not computed in four cases, because the transverse diameter of the chest, or of the heart, or both, could not be measured. In nineteen (14.7 per cent), the cardiothoracic ratio was the same by both methods. In twenty-five (19.4 per cent), the cardiothoracic ratio in the orthodiagram was .01 larger, in twenty (15.5 per cent), .02 larger, in twenty-four (18.6 per cent), .03 larger, in eighteen (14.8 per cent), .04 larger, in twelve (9.3 per cent), .05 larger, and in eleven (8.5 per cent), varied from .06 to .09 larger (Fig. 4). In ninety-six (74.4 per cent), the cardiothoracic ratio in the orthodiagram was .01 to .05 larger than in the teleoroentgenogram.

The diameter of the aorta was compared in 124 cases (Fig. 1*C*). In only five cases (4 per cent) was the Vaquez-Bordet diameter the same in the orthodiagram and teleoroentgenogram; in all others the latter showed a larger diameter, and the enlargement varied from 2 per cent to 27 per cent. In seventy-eight (62.9 per cent), the enlargement was between 6 per cent and 15 per cent, and, in fourteen (11.3 per cent), the enlargement varied from 16 per cent to 20 per cent. In three (2.4 per cent), the enlargement was over 20 per cent. In any given subject, the object-film distance of the descending aorta in the posteroanterior view is greater than that of other parts of the heart, including the ascending aorta; it is to be expected, therefore, that the greatest magnification would occur here.

DISCUSSION

Examination of Tables I and II shows that magnification of the size of the heart in teleoroentgenograms is considerable; even at a distance of 6½ feet the error is sufficiently great to cause considerable magnification. With proper centering, magnification is dependent upon target-film and object-film distances. The error incident to these factors can be computed for a flat object by the following formula: Error (X) is to the actual size of object as the object-film distance is to the target-object distance. Using the measurements in Fig. 5, the error (X) is determined by the following equation:

$$X : 12 :: 5 : 67$$
$$X = .9$$

The magnification, therefore, is 7.5 per cent. It is apparent that the less the target-film distance, the object-film distance remaining the same, the greater the magnification. Conversely, the less the object-film distance, the target-film distance remaining the same, the less the magnification. If the above distances remain the same, the larger the object, the greater the actual error (X); the percentage difference, however, remains the same.

When dealing with an asymmetrical object such as the heart, the object-film distance will vary slightly for different portions. According to Roesler,[2] the distance of the left lower pole of the heart from the front of the chest averages 3 to 4.5 cm.; that of the right border averages 4 to 6 cm., that of the ascending aorta, 5 to 7 cm., and that of the pulmonary artery, 5 cm. The enlargement of the cardiac silhouette is therefore unequally distributed, and as a result, the silhouette is distorted (Fig. 6*A*). Distortion of a normal heart in a normal chest is admittedly slight, but in the obese or in patients with chest deformities this may be accentuated. In Fig. 6*B*, tracings of teleoroentgenograms of a model, taken at different object-film distances, are superimposed; the degree of magnification is unequally distributed, and, consequently, the shape of the heart is slightly altered. There was no additional error caused by improper centering, for the target was centered upon the center of the model; clinically, if the target is centered upon the center of the chest, the distortion of the cardiac silhouette may be increased.

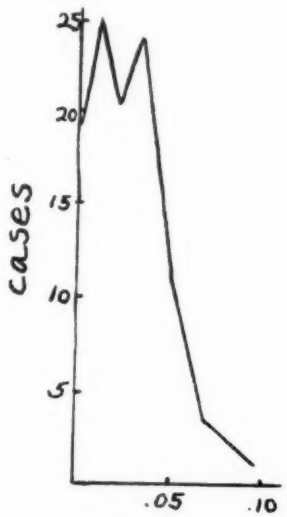

Fig. 4.

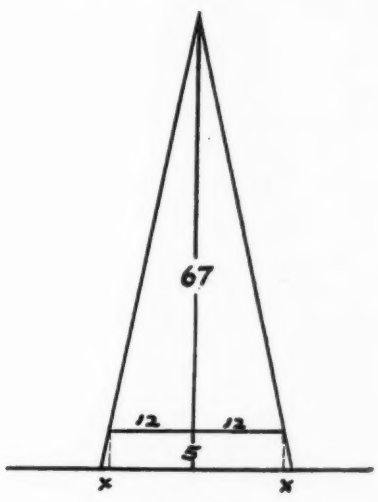

Fig. 5.

Fig. 4.—Magnification of cardiothoracic ratios obtained from orthodiagrams compared with those from teleoroentgenograms.

When the shape of the chest is normal, its greatest, or projected, diameter is considerably more posterior than the greatest, or projected, diameter of the heart. The distance from the plane of the greatest diameter of the bony thorax to the front of the bony thorax at the level of the nipple was measured in fifteen cadavers, and varied from 7 to 11.7 cm. In the living, the distance (object-film distance) of the projected diameter is further increased by the thickness of the overlying tissues. It is therefore apparent that, in roentgenograms, the percentage magnification of the chest is greater than that of the heart, because the object-film distance of the projected diameter is greater (Fig. 2). In

deformed, or in deep, chests, in which the object-film distance of the greatest diameter is unusually large, the magnification will be increased, and, in the former, the enlargement may be unequal, and, consequently, the silhouette will be distorted (Fig. 3).

Inasmuch as the degree of magnification of the chest is greater than that of the heart in teleoroentgenograms, the cardiothoracic ratio obtained by the latter method of examination is usually smaller than that obtained by orthodiagraphy (Fig. 4). In teleoroentgenograms, the cardiothoracic ratio is not only dependent upon the diameter of the heart and chest, but also upon the distance of the projected diameters from the film. In deep chests, or in deformed chests, in which the projected diameter of the chest is more posterior than normal, the increased magnification of the chest as the result of this factor may be considerable and may more than counterbalance the effect of slight magnification of the heart upon the cardiothoracic ratio. In these chests, therefore, the cardiothoracic ratio may be within normal limits when the heart is actually enlarged. The importance of the object-film distance of the projected diameters of the heart and chest can be illustrated by comparing anteroposterior views with posteroanterior views. In Fig. 6*C*, the teleoroentgenograms (anteroposterior and posteroanterior views) of a man, aged 48, who was suffering from syphilitic aortitis, are superimposed. The films were exposed consecutively at a distance of seventy-eight inches; the chest was of average depth. The transverse diameters of the chest and heart vary considerably; the heart appears larger in the anteroposterior view, and the chest appears larger in the posteroanterior. As a result, the cardiothoracic ratio is .61 in the anteroposterior view, and .51 in the posteroanterior view. It is clear, therefore, that, in teleoroentgenograms, the cardiothoracic ratio is not only dependent upon the diameter of the heart and chest, but is also influenced by the shape of the chest. In orthodiagrams the latter factor is not operative.

In addition to differences resulting from unequal magnification of the heart and chest, the cardiothoracic ratio is also influenced by respiration, and by the position of the chest in relationship to the fluoroscopic screen or film. The phase of respiration is of particular importance. During inspiration, the transverse diameter of the chest increases, the heart usually assumes a more vertical position because of the descent of the diaphragm, and, as a result, the transverse diameter of the heart is decreased, with a consequent decrease in cardiothoracic ratio. Conversely, during expiration, the transverse diameter of the chest decreases, the heart assumes a more horizontal position and its transverse diameter is increased, and the cardiothoracic ratio is therefore larger. It is, therefore, obvious that cardiothoracic ratios obtained from teleoroentgenographic measurements are not only influenced by divergent rays, but also by the phase

of respiration. The effect of the phase of the cardiac cycle and position of the chest is apparent, and requires no further explanation.

Comparison of the measurements obtained in 133 cases with those of the model shows that in teleoroentgenograms the greatest magnification is of the aorta. Table II shows measurements obtained from roentgenograms of the model at varying target-film and object-film distances. Although the error at a distance of 6½ feet is considerable, especially with increased object-film distances, at sixty and forty-eight inches, provided the object-film distance remains the same, the magnification is considerably greater. The aorta is magnified most, but this is obvious because the descending aorta is farthest from the film. The greater

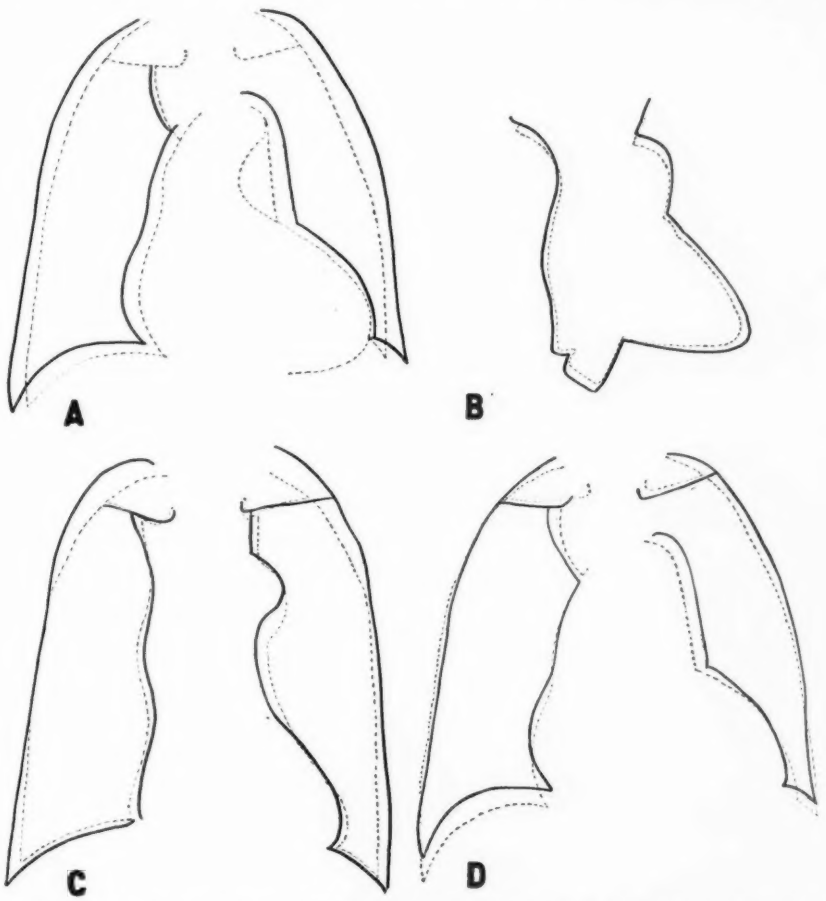

Fig. 6.—*A*, Orthodiagram (dotted line), and outline of teleoroentgenogram (solid line), taken at seventy-eight inches, of patient with hypertension and arteriosclerosis, superimposed. The two were made consecutively. *B*, Outlines of teleoroentgenograms of model of heart, taken at seventy-eight inches, with an object-film distance of two inches (dotted line) and five inches (solid line), superimposed. *C*, Outlines of teleoroentgenograms taken at seventy-eight inches, of patient suffering from syphilitic aortitis, superimposed; solid line is posteroanterior view, dotted line is anteroposterior view. The two were made consecutively. *D*, Outlines of teleoroentgenograms taken at seventy-eight inches of same patient as in Fig. 6*A*, superimposed. Solid line is posteroanterior view; dotted line is anteroposterior view.

magnification of the aorta, as compared with the heart, is therefore primarily the result of greater magnification of the descending aorta. In the model, the descending aorta was only 2.2 inches from the anterior surface of the heart. Clinically, therefore, the elongated, uncoiled aorta in an emphysematous or kyphotic chest should be even more magnified, because in these cases the depth of the chest and, therefore, the distance of the descending aorta from the front of the chest are greatly increased. It has been shown that even in severe kyphoscoliosis, regardless of the position of the heart in relation to the spine, the descending aorta closely follows the spine.

Inasmuch as the object-film distance in the posteroanterior view is greater for the descending aorta than for the ascending aorta, it is obvious that, in teleoroentgenograms, not only is the aorta magnified, but the magnification is unequal. The "uncoiled" aorta in Fig. 6*D* appears to be wider in the posteroanterior view than in the anteroposterior, and the significant changes are confined to the descending aorta. Inasmuch as the target-film distance of the chest as a whole was not changed, and the position of the chest in relation to the film was approximately the same, the change in the diameter of the aorta in this case can be caused only by a change in the object-film distance of the descending aorta; the latter is smaller in the anteroposterior view. The converse occurs in the case of syphilitic aortitis (Fig. 6*C*), with dilatation of the ascending and transverse portions of the aortic arch. The distortion of the aorta is greatest in the anteroposterior view, probably because the object-film distance of the involved portions of the aorta is greater in this view.

In carefully drawn orthodiagrams, the factors causing distortion are not operative because the target is not stationary and parallel rays are

TABLE II

TRANSVERSE DIAMETER (CM).

OBJECT-FILM DISTANCE OF HEART	ACTUAL MEASUREMENT	TARGET-FILM DISTANCE			PER CENT DIFFERENCE		
		78″	60″	48″	78″	60″	48″
2 inches	12.5	13.2	13.4	13.5	5.6	7.2	8.0
3 inches	12.5	13.4	13.6	14.0	7.2	8.8	12.0
4 inches	12.5	13.6	13.9	14.3	8.8	11.2	14.4
5 inches	12.5			14.8			18.2
6 inches	12.5			15.0			20.0

AORTA VAQUEZ-BORDET (CM.)

OBJECT-FILM DISTANCE OF AORTA	ACTUAL MEASUREMENT	TARGET-FILM DISTANCE			PER CENT DIFFERENCE		
		78″	60″	48″	78″	60″	48″
4.2 inches	9.0	9.7	9.8	10.1	7.8	8.9	12.2
5.2 inches	9.0	9.9	10.1	10.3	10.0	12.2	14.4
6.2 inches	9.0	10.0	10.4	10.7	11.1	15.6	18.9
7.2 inches	9.0			10.8			20.0
8.2 inches	9.0			11.1			23.3

used. Although great difference of opinion exists as to the relative merits of the two methods of examination, most authorities agree that measurements obtained by careful orthodiagraphy are more accurate than those by teleoroentgenography. Although, as stated above, it is not possible to compare orthodiagrams and teleoroentgenograms with any degree of accuracy because of the factors which may cause distortion and magnification, measurements obtained by the two methods of examination of the model of the heart, in which these factors are eliminated, indicate that orthodiagrams, when properly done, are more accurate than teleoroentgenograms. However, if teleoroentgenograms are made at a distance of not less than 72 inches, and if the subject is neither obese nor has a thick or deformed chest, the differences in measurement are usually not great enough to be of clinical importance.

SUMMARY AND CONCLUSIONS

1. Measurements of orthodiagrams were compared with those of teleoroentgenograms, taken at a distance of seventy-eight inches, in 133 consecutive cases. In each instance, the teleoroentgenogram was taken immediately after the orthodiagram had been made.

2. In 130 cases, the transverse diameter of the heart averaged 6.6 per cent larger in the teleoroentgenograms, with a range from 0 to 16 per cent. The comparison may not be accurate because (1) the position of the chest, (2) the phase and depth of respiration, and (3) the phase of the cardiac cycle may have varied in the two methods of examination.

3. The transverse diameter of a model of the heart was considerably magnified in the teleoroentgenograms. At a target-film distance of seventy-eight inches and an object-film distance of two inches, the magnification was 5.6 per cent; at three inches, 7.2 per cent; and at four inches, 8.8 per cent. The magnification increased with a decrease in the target-film distance; at forty-eight inches, with an object-film distance of four inches, it was 14.4 per cent.

4. The transverse diameter of the chest averaged 11.1 per cent larger in teleoroentgenograms, with a range from 2 to 20 per cent.

5. The cardiothoracic ratio was usually smaller in the teleoroentgenograms than in the orthodiagrams. In 110 of 129 cases, the cardiothoracic ratio was .01 to .09 greater in the orthodiagrams; in nineteen, the cardiothoracic ratio was the same as that in the teleoroentgenograms.

6. In 119 of 124 cases, the Vaquez-Bordet diameter of the aorta was larger in the teleoroentgenograms, varying from 2 to 27 per cent; in seventy-eight (62.9 per cent), the magnification varied from 6 to 15 per cent. In fourteen (11.3 per cent), the magnification varied from 6 to 20 per cent. In five cases (4 per cent) the diameters were the same.

7. At a target-film distance of seventy-eight inches, with the model of the heart two inches from the film (aorta, 4.2 inches), the increase in

the Vaquez-Bordet diameter was 7.8 per cent; at four inches (aorta, 6.2 inches), it was 11.1 per cent. At a target-film distance of forty-eight inches, the increase was 12.2 per cent at two inches (aorta, 4.2 inches), and 18.9 per cent at four inches (aorta, 6.2 inches).

8. Inasmuch as the magnification is dependent upon object-film distance and target-film distance, the variation of the former in different parts of the heart and aorta would cause an unequal distribution of the magnification, and, therefore, the shape would be altered. The distortion of the heart is not great and is of little practical significance. The aorta, however, may be considerably magnified and distorted, especially in deep chests, in which the object-film distance of the descending aorta is increased.

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A COMPARATIVE STUDY OF NORMAL AND ABNORMAL BLOOD PRESSURES AMONG UNIVERSITY STUDENTS, INCLUDING THE COLD-PRESSOR TEST*

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MANY cases of hypertension and hypotension are of obscure origin. Consequently, the significance of these supposedly abnormal blood pressures is still vague and indefinite.

In order that a proper interpretation of abnormal blood pressure readings may be made, it is necessary to know the physiology of blood pressure. We are acquainted with most of the factors which govern blood pressure, i.e., the elasticity of the arteries, the autonomic nervous system, the rate of the heartbeat, the blood volume, and certain endocrine secretions. Pathologic conditions, such as hyperthyroidism, toxemias of pregnancy, foci of infection, tumors of the spinal cord and suprarenal gland, increased intracranial pressure, and some cases of arteriosclerosis and nephritis have been definite factors in the production of arterial hypertension. It has been known for some time that hypotension is frequently associated with such chronic, wasting diseases as tuberculosis, cancer, anemia, typhoid fever, and Addison's disease, as well as hypoadrenia, hypothyroidism, and the neurasthenic syndrome.

There are several classifications of conditions associated with high and low blood pressure, but they all agree on one group, in which all cases in which there are no apparent causative factors are placed. These patients are said to have an essential hypertension or hypotension. In other words, no apparent reason can be found for the abnormal blood pressure—at least with our present knowledge of the subject.

This investigation was undertaken in order to study the normal and apparently abnormal blood pressures among university students. A history and physical examination was obtained on each entering student. This study included observations on 15,500 male students at the University of Illinois, from 1935 to 1939. Those with high or low blood pressure, as well as normal controls, were re-examined at intervals, and the following information obtained from them:

Name_____. Class_____. Wt._____. Pulse_____.
Date of entrance_____. Blood pressure_____. Duration_____.
Age_____. Ht._____. Descent_____.
Family history (particularly pertaining to cardiovascular disease, high and low blood pressure).
Illness_____. Operations_____.
Work—Mental_____, Physical_____.
Habits—Eating rate_____, Amount eaten_____.
Bowels_____. Weight change_____.
Amount of exercise_____.

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Amount of sleep_____ Emotions_____
Use of coffee (over 1 cup daily)_____
Tobacco (more than 6 cigarettes, pipes, chews)_____
Physical examination

The students with a systolic blood pressure of more than 150 mm. Hg at the time of their entrance examination were put into the hypertension group. All students with a systolic pressure, upon entrance, below 108 were classified, for this investigation, as having hypotension. The normal, or control, group consisted of matriculants with a systolic blood pressure between 114 and 138 mm. Hg. The cold-pressor test was not done in discernible cases of organic heart, kidney, or thyroid disease.

The cold-pressor test technique, as described by Hines and Brown,[1] was used to study the vasomotor reactions of ninety-six hypertensive, 128 normal, and fifty-six hypotensive, subjects. Two variations of this technique were made. The hand was kept in ice water until the maximum rise in blood pressure was reached. It required about three minutes, in a few cases, to reach the peak. Thirty students were tested in the reclining position, according to the method of Hines and Brown. These same students were also tested in the sitting position. A comfortable chair was provided, with a table of convenient height on one side for the sphygmomanometer, and a stool on the other side for the ice water container. Following the rest period, it was found that the basal blood pressure readings and the response to the cold-pressor test in the two positions checked with each other. Consequently, the remaining tests were all done with the subject in the sitting position. This position has the advantage of making the test available to all physicians, even in small offices in which facilities for carrying out the test in a reclining position are inadequate. Most examining tables are too hard and uncomfortable to be used for this type of study.

A comparative study of the three groups revealed that 73 per cent of the subjects with normal blood pressure showed the maximum systolic increase within one minute, whereas only 49.9 per cent of the hypertensive and hypotensive groups showed the maximum response within that time (Table I). By the end of two minutes, all of the normal and hypotensive subjects had attained this maximum increase, as compared to 86.8 per cent of the hypertensive group. It will be noted that the diastolic pressures in the three groups closely paralleled the systolic pressures.

Another interesting aspect of this vasomotor response to the cold test was that the systolic pressure of only 24.4 per cent of the hypertensive subjects increased from 1 to 10 mm. Hg, as compared to 63 per cent and 41.6 per cent of the normal and hypotensive subjects, respectively (Table II). Seventeen and seven-tenths per cent of the hypertensive group showed increases ranging from 21 to 30 mm. Hg, in contrast to 7.4 per cent of the normal subjects and none of the hypotensive group. The average maximal increase in the systolic pressure in the hypertensive, normal, and hypotensive groups was 18, 10.4, and 11 mm. Hg, respectively. The diastolic pressure increased about the same as the systolic pressure, with the exception that, in the normal group, the diastolic pressure increased, on the average, 3.3 mm. Hg more than the systolic pressure.

TABLE I

TIME REQUIRED FOR MAXIMUM RESPONSES OF BLOOD PRESSURE TO COLD TEST

BLOOD PRESSURE	TIME IN MINUTES						
	½	1	1½	2	2½	3	4
High							
Systolic	15.2*	34.7	4.3	32.6	4.4	9.7	
Diastolic	26.6	17.7	8.8	31.0	4.4	8.8	2.2
Normal							
Systolic	46.1	26.9	19.2	7.7			
Diastolic	19.2	34.6	15.3	26.9	3.8		
Low							
Systolic	8.3	41.6	8.3	41.6			
Diastolic	8.3	41.6	0	41.6	8.3		

*All figures represent per cent of subjects studied.

TABLE II

THE INCREASE OF THE SYSTOLIC BLOOD PRESSURE IN RESPONSE TO THE COLD TEST

BLOOD PRESSURE	MM. OF HG INCREASE					
	0	1-10	11-20	21-30	31-40	AVERAGE INCREASE
High						
Systolic	2.2*	24.4	46.6	17.7	8.8	18.0
Diastolic	2.3	26.7	26.7	37.3	6.9	17.0
Normal						
Systolic	3.7	63.0	25.9	7.4	0	10.4
Diastolic	11.1	33.3	33.3	14.8	7.4	13.7
Low						
Systolic	0	41.6	58.3	0	0	11.0
Diastolic	0	50.0	50.0	0	0	11.0

*All figures represent per cent of subjects studied, except last vertical column, which gives Mm. Hg.

The systolic pressures in the normal group had a definite tendency to return to the basal level faster than in the hypertensive and hypotensive groups (Table III). Within three minutes after the cold test was begun, the systolic pressures of 62.8 per cent of the normal subjects had returned to the basal level, as compared to only 31 per cent and 24.9 per cent, respectively, of the hypertensive and hypotensive subjects. In fact, seven to eight minutes elapsed before the systolic pressures of all subjects in the latter groups returned to their initial level. Ninety-six and two-tenths per cent of the diastolic pressures in the normal group returned to the basal level within four minutes, as compared to 56.7 per cent and 58.2 per cent, respectively, in the hypertensive and hypotensive groups.

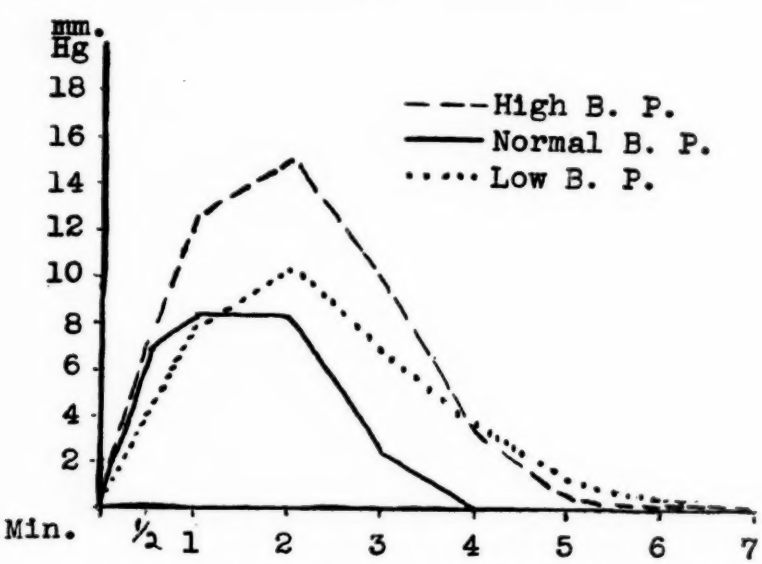
From Graphs I and II, which record the average increase in the systolic and diastolic pressures, and the duration of the increase, for each group, it is apparent that:

1. The hypertensive and hypotensive subjects were slower in reaching their maximum increase in the systolic and diastolic pressures.
2. There was a greater increase in the systolic and diastolic pressures of the hypertensive subjects than in the control group.

3. The hypertensive and hypotensive subjects returned to their basal level more slowly than did the normal subjects.

Hines and Brown[1] observed no relationship between sensitivity to ice water and blood pressure response. They explain the mechanism as a widespread vasomotor reaction initiated through the neurogenic arc. According to these authors, the reaction is not mediated by an adrenal hormone, for it occurs in adrenalectomized dogs and in Addison's disease, and, also, when a tourniquet is placed around the arm which is in the ice water. They found that the maximum response usually occurred within the first thirty seconds, and, in normal subjects, that the blood pressure returned to the basal level within two minutes. In the present investigation, the maximum response usually occurred between one and two minutes, after which the pressure dropped to the basal level in the normal group in about four minutes (Graph I). Just why there should be this difference is not clear, unless age is a factor. The ages of these students ranged from 17 to 24 years.

Table IV summarizes the averages of the blood pressure observations.

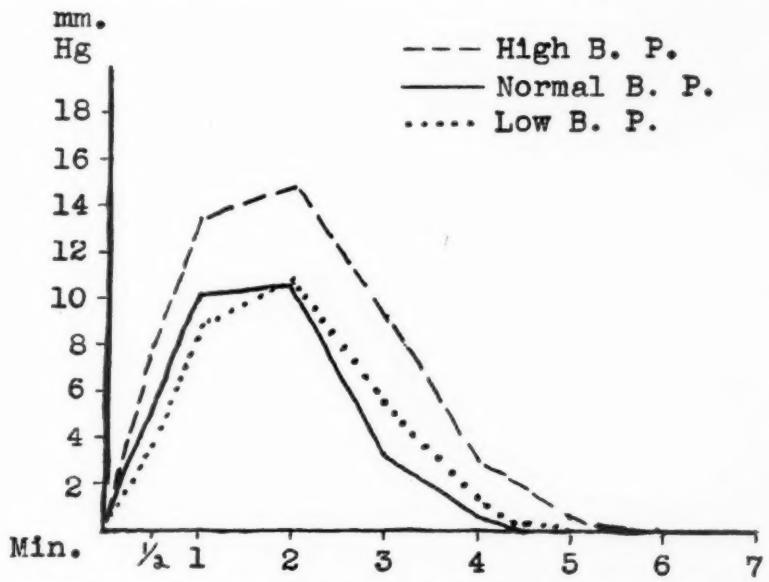


Graph I.—Increase in the systolic blood pressure during the cold test.

In the vertical column, designated as mm. Hg, there are, for each group, the average basal, usual, and maximum blood pressure increases produced by the cold test. The usual blood pressure was determined by the average of repeated measurements before subjects began the rest period prior to the cold test. The differences between the usual and basal systolic blood pressure in the hypotensive and normal groups were only 5 and 7 mm., respectively, in contrast to a difference of 28 mm. in the hypertensive group. There was a difference between the basal and

usual systolic pressure in the hypertensive group of 10 mm. more than the maximum increase produced by the cold test. This marked variation between the basal level and the usual pressure is a definite aid in detecting hyperreactors, particularly when it is confirmed by the results of the cold test. The diastolic pressure response to the cold test in the three groups was approximately the same as that of the systolic blood pressure. The difference between the basal and usual diastolic pressures in the hypertensive group was far below the difference noted in the systolic pressures.

The detailed histories obtained from the students in this investigation brought forth some interesting points (Table V). Forty-three and seven-



Graph II.—Increase in the diastolic blood pressure during the cold test.

tenths per cent of the hypertensive subjects, as compared with only 11.7 per cent and 14.3 per cent, respectively, of the normal and hypotensive subjects, stated that they were nervous or easily excited. A family history of hypertensive cardiovascular disease was obtained from 54.1 per cent of the hypertensive subjects, as contrasted with 3.1 per cent in the normal, and 5.3 per cent in the hypotensive, groups. It was also noted that 17.8 per cent of the hypotensive subjects gave a history of familial hypotension, whereas none of the hypertensive subjects, and only 2.3 per cent of the normal subjects, indicated that members of their immediate family or of preceding generations had had low blood pressure.

Hines[2] and Brown[3] noted that a family history of hypertensive cardiovascular disease was five times as frequent among persons who had high

TABLE III

TIME REQUIRED FOR BLOOD PRESSURE TO RETURN TO BASAL LEVEL DURING COLD TEST

BLOOD PRESSURE	TIME IN MINUTES								
	0	1	2	3	4	5	6	7	8
High									
Systolic	2.2*	0	4.4	24.4	22.2	29.0	11.1	4.2	2.2
Total†	2.2	2.2	6.6	31.0	53.2	82.2	93.3	97.5	99.7
Diastolic	2.2	0	0	20.5	34.0	27.2	16.0		
Total	2.2	2.2	2.2	22.7	56.7	83.9	99.9		
Normal									
Systolic	3.7	3.7	11.0	44.4	29.6	3.7	3.7		
Total	3.7	7.4	18.4	62.8	92.4	96.1	99.8		
Diastolic	11.1	7.4	11.1	37.0	29.6	0	3.7		
Total	11.1	18.5	29.6	66.6	96.2	96.2	99.9		
Low									
Systolic	0	0	8.3	16.6	16.6	25.0	25.0	8.3	
Total	0	0	8.3	24.9	41.5	66.5	91.5	99.8	
Diastolic	0	0	0	41.6	16.6	25.0	16.6		
Total	0	0	0	41.6	58.2	83.2	99.8		

*All figures represent per cent of subjects studied.
†Accumulative total for each successive minute.

TABLE IV

SUMMARY OF BLOOD PRESSURE VARIATIONS FROM THE BASAL LEVEL

	SYSTOLIC BLOOD PRESSURE						DIASTOLIC BLOOD PRESSURE					
	L. B. P.*		N. B. P.*		H. B. P.*		L. B. P.		N. B. P.		H. B. P.	
	MM. HG	RISE MM. HG	MM. HG	RISE MM. HG	MM. HG	RISE MM. HG	MM. HG	RISE MM. HG	MM. HG	RISE MM. HG	MM. HG	RISE MM. HG
Basal B. P.	99		116		136		70		74		80	
Usual B. P.	104	5	123	7	164	28	75	5	77	3	87	7
B. P. with Cold Test	110	11	126	10	154	18	81	11	88	14	96	16

*L. B. P. indicates low blood pressure group.
N. B. P. indicates normal blood pressure group.
H. B. P. indicates high blood pressure group.

blood pressure or were hyperreactors to the cold test as it was among subjects who reacted normally to the test. The results in Table V certainly compare favorably with those of these authors. It was suggested long ago that a tendency to essential hypertension might possibly be hereditary. Recent, concrete evidence has substantiated this belief. The type of blood pressure reaction in many cases follows a definite hereditary pattern, whether it be high or low. Perhaps this depends, for the most part, upon some structural or physiologic peculiarities of the autonomic nervous system or endocrine system which are passed through the germ plasm from one generation to the next.

The quantity of food eaten may have something to do with hypertension, for there were well over twice as many heavy eaters in the hypertensive group as in the other two groups. The amount of exercise, apparently, is not a factor in the production of essential hypertension.

TABLE V

DETAILS OF HISTORIES OF SUBJECTS OF THIS STUDY

	PER CENT WITH H. B. P.*	PER CENT WITH N. B. P.*	PER CENT WITH L. B. P.*
Emotions			
Nervous and excitable	43.7	11.7	14.3
Stable	56.3	88.2	85.7
H.B.P. in family	54.1	3.1	5.3
L.B.P. in family	0	2.3	17.8
Foci of infection on physical examination	18.7	26.5	8.9
Constipation	4.1	6.2	7.1
Rate of Eating			
Rapid	44.7	11.7	42.8
Moderate	41.6	76.6	50.0
Slow	13.5	11.7	7.1
Quantity Eaten			
Heavy eater	35.4	14.8	14.3
Medium eater	63.5	78.9	78.5
Light eater	1.1	6.2	7.1
Exercise			
Vigorous	6.2	6.2	7.1
Moderate	40.6	35.1	50.0
Mild	53.1	58.5	42.8
Stimulants			
Tobacco	16.6	19.5	50.0
Coffee	12.5	11.7	28.5

*H. B. P. indicates high blood pressure.
N. B. P. indicates normal blood pressure.
L. B. P. indicates low blood pressure.

Tobacco (more than six cigarettes, cigars, pipes, or chews) and coffee (more than one cup daily) were used by two to three times as many students in the hypotensive group as in the other two groups.

Patients are frequently told, after the first measurement, that they have high or low blood pressure. Note that the blood pressure of 64.8 per cent of the students who had a systolic pressure above 150 mm. at the time of their entrance physical examination was normal at the time of the first re-examination. After the third blood pressure measurement, 75 per cent were well within normal limits (Table VI). Many of these students were hyperreactors to the cold test, but, in the present state of our knowledge, by far the most of them must still be considered normal. Certainly, excitement, nervousness, a sense of uncertainty, new environmental adjustments, or other psychologic factors must have had something to do with producing most of these high systolic blood pressure readings. Reisman[4] believes that economic and domestic worries may cause a temporary or permanent rise of blood pressure. Grollman[5] found that an increase in the pulse rate and blood pressure occurred following psychic disturbances. Just how this action occurs is still a matter of conjecture. Does an increase in the secretion of adrenalin or pituitrin take place? Does the autonomic nervous system produce a spastic constriction of the arterioles, or can it be explained by the intrinsic myogenic

capacity of the blood vessels to contract and dilate? When the hypotensive subjects returned for their re-examination, 82.2 per cent were within normal limits (Table VI).

TABLE VI

STUDENTS WITH ABNORMAL SYSTOLIC BLOOD PRESSURE UPON ENTRANCE PHYSICAL EXAMINATION AND RESULTS OF SUBSEQUENT EXAMINATIONS

BLOOD PRESSURE	ABOVE 150 MM. HG UPON ENTRANCE		BELOW 104 MM. HG UPON ENTRANCE	
	NO. OF STUDENTS	PER CENT OF STUDENTS	NO. OF STUDENTS	PER CENT OF STUDENTS
Remained unchanged	96	24.8	56	17.6
To normal at first recheck	251	64.8	192	60.5
To normal at second recheck	25	6.4	69	21.7
To normal at third recheck	15	3.9	0	0
Total rechecked	387		317	
Not rechecked	132	25.4	74	18.9
Total	519		391	

The most important factor controlling blood pressure centers around the autonomic nervous system. When the sympathetics and parasympathetics are in a state of balance, a normal pressure results. When the impulses over the nervous pathways to the heart are in balance, the heart beats regularly and at a normal rate. If this equilibrium is disturbed, the heart rate changes, and the change depends upon which pathway carries the greater number of impulses. So it is with blood pressure; if this balance is disturbed, a hypertonic or hypotonic state occurs, and more impulses or impulses of greater intensity are sent over the vasopressor or vasodepressor nerve fibers, as the case may be. Whether this regulation is governed by the carotid sinus, or initiated through the neurogenic arc, or by an intrinsic myogenic factor, or entirely by hormonal stimulation, or by unknown regulatory centers has not been established definitely. A combination of these factors may be operative. Some evidence has been produced by Zipf[6] and Goerner and Haley[7] that depressor substances may also be present in the body fluids. DeGroat and his associates,[8] experimenting on animals, were able to produce hypertension by denervating the carotid sinuses and sectioning the depressor nerves.

SUMMARY

The blood pressure reactions to a standard cold stimulus of students with high, normal, and low blood pressure were noted. A careful history, physical examination, and re-examination were obtained on students with normal and abnormal blood pressure.

1. With the application of the standard cold test, the normal subjects reached the maximum increase in the systolic and diastolic blood pressure sooner than the hypertensive and hypotensive subjects.

2. There was a greater increase in the systolic and diastolic blood pressure in the hypertensive group than in the control group.

3. The blood pressure of the hypotensive and hypertensive subjects returned to the basal level more slowly than did that of the normal subjects.

4. There was a far greater difference between the usual systolic blood pressure and the basal blood pressure in the hypertensive group than in the normal and hypotensive groups. This criterion is a definite aid in discovering hyperreactors, especially when it is confirmed by the cold test.

5. The same factors which govern the emotional status of individuals play an important part in their blood pressure reactions.

6. There is a definite hereditary factor in the regulation of blood pressure. The tendency toward essential hypertension or hypotension is carried by the germ plasm from one generation to the next.

7. The percentage of heavy eaters in the hypertensive group was over twice as great as in the normal and hypotensive group.

8. The amount of work or exercise is apparently not an etiologic factor in the production of essential hypertension.

9. Tobacco and coffee were used by two to three times as many students in the hypotensive group as in the other two groups.

10. At least two or three subsequent examinations should be made before a person is classified as having hypertension or hypotension. This will prevent worry and anxiety in certain cases, and will be of definite value to the physician in arriving at a definite diagnosis.

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STUDIES IN HYPERTENSIVE HEART DISEASE

IV. Factors in the Production of Congestive Failure

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IT IS known that a number of factors may contribute to heart failure in the course of hypertensive heart disease. The relative importance of these factors, however, has not been established. It is maintained, on the one hand, that myocardial weakness in hypertensive heart disease is due primarily to factors resulting from the hypertension itself, and, on the other, to concomitant coronary disease. The purpose of the present study is to throw some light on the relative importance of these factors.

METHOD

It appeared that the significance of the hypertensive factors could best be evaluated by comparing the cardiac abnormalities in this type of heart failure with those in cases in which there was no hypertension. Therefore, two groups of patients were studied: 137 with hypertension, and 324 without hypertension. Patients were considered to have hypertension when their systolic and diastolic pressures were consistently above 150 and 90 mm. of mercury, respectively. Patients with congestive failure associated with diabetes, thyrotoxicosis, anemia, pregnancy, uncontrolled auricular fibrillation, and heart disease of congenital, rheumatic, or syphilitic origin were excluded. Congestive failure was present in forty-nine of the patients with hypertension, and in thirty-one of the patients who did not have hypertension. Among the latter there were six cases of cor pulmonale, with extensive pulmonary disease, right ventricular failure, and hypertrophy of the right ventricle (necropsy). These were considered as probably examples of hypertension of the lesser circulation, and were therefore excluded. There remained, for comparison, twenty-five patients without hypertension. In each case the diagnosis of congestive failure was based either on a history of attacks of cardiac asthma or pulmonary edema, or on objective evidence, such as prolongation of the circulation time, râles at the bases of the lungs, peripheral edema, enlargement of the liver, and accumulations of fluid in the serous cavities. Rigid criteria were used in the classification of the degree of coronary artery disease. The atherosclerosis was considered slight when the intimal changes were few and scattered, or entirely absent; as moderate, when the intimal surfaces were covered with many plaques, but the process had produced but little or no narrowing of the lumen; and as marked, when there was extreme narrowing or occlusion of the major branches.*

Patients Without Hypertension.—Marked coronary disease was present in twenty-three of the twenty-five patients without hypertension (90 per cent). Nineteen of these had occlusion of one major coronary artery,

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*Major branches refer to main stems of left anterior descending, left circumflex, and right coronary arteries.

and fifteen had an occlusion of one, with marked narrowing or occlusion of at least one other, major artery (Table II). In two cases (24, 25) the heart failure was apparently not caused by coronary disease. One of these patients (24) showed a slight degree of atherosclerotic aortic stenosis, and this may have contributed to his heart failure.

It will be noted that five of the patients in this group showed varying degrees of atherosclerotic aortic stenosis (Table II). Four of these also showed marked coronary disease. If we exclude these five patients from the series, nineteen of the remaining twenty patients (95 per cent) showed marked coronary disease, and sixteen (80 per cent) had occlusions of one or more major branches.

TABLE I

PATIENTS WITH CONGESTIVE FAILURE

DATA	WITH HYPERTENSION		WITHOUT HYPERTENSION	
TOTAL NUMBER OF CASES	49	100%	25	100%
Age Distribution				
30-49 years	5	10.2%	0	-
50-59 years	10	20.4%	6	24.0%
60-69 years	21	42.8%	10	40.0%
70- years	13	26.6%	9	36.0%
Sex:				
Males	38	77.6%	22	88.0%
Females	11	22.4%	3	12.0%
Severe Coronary Disease	26	53.1%	23	90.0%
Moderate Coronary Disease	16	32.7%	2	8.0%
Slight Coronary Disease	7	14.2%	0	-
Patients with Coronary Occlusion	16	32.7%	19	76.0%
Patients with Cardiac Infarction	10	20.4%	14	56.0%
Old Infarcts	5	10.2%	12	48.0%
Recent Infarcts	5	10.2%	2	8.0%
Patients with Cardiac Asthma	27	55.1%	5	20.0%
Patients with Angina Pectoris	22	44.9%	12	48.0%
Angina Pectoris prior to C.F.	18	36.7%	11	44.0%
Angina Pectoris after C.F.	4	8.2%	1	4.0%
Duration of Cardiac Symptoms				
Less than 1 year	5	10.2%	4	16.0%
1-5 years	27	55.1%	14	56.0%
5-10 years	17	34.7%	7	28.0%
Duration of Congestive Failure				
Less than 6 months	24	49.0%	8	32.0%
6 months to 2 years	17	34.7%	15	60.0%
Over 2 years	8	16.3%	2	8.0%

Patients With Hypertension.—Twenty-six of the forty-nine patients with hypertension and congestive failure had marked coronary disease. Sixteen of these had occlusion of one major coronary branch, and ten had an occlusion of one, with marked narrowing or occlusion of at least one other, major artery (Table III). The degree of coronary disease in twenty-three cases (47 per cent), however, was classified as slight or moderate, for in these cases there was no demonstrable interference with the circulation through the major coronary arteries. The heart weights

TABLE II

PATIENTS WITHOUT HYPERTENSION MANIFESTING CONGESTIVE FAILURE

NO.	AGE	SEX	HEART WEIGHT GM.	DEGREE COR. DIS.	VESSELS OCCLUDED			INFARCTS		ANGINA PECTORIS	CARDIAC ASTHMA	CLINICAL C.T.	DURATION OF SYMPTOMS	DURATION OF FAILURE
					L.A.D.	L.C.	R.C.	OLD	RECENT					
1	90	F	490	3	N	0	N	0	0	0	0	0	2 weeks	2 weeks
2	80	M	620*	3	+	N	+	0	0	0	0	0	4 years	Few wk.
3	88	M	420	3	+	N	N	0	0	0	+	0	Few yr.	2 yr.
4	68	F	310	3	N	0	0	0	0	0	0	0	Several yr.	1 week
5	85	M	530	3	N	0	N	#	#	+	0	0	4 mo.	6 wk.
6	82	F	580*	3	0	N	0	0	0	0	0	0	2 yr.	3 mo.
7	80	M	530	3	+	0	0	0	0	+	0	+	4 yr.	3 yr.
8	74	M	720*	3	+	0	0	+	0	0	0	0	3 yr.	7 mo.
9	67	M	540	3	+	N	N	+	0	+	0	+	5 yr.	2 yr.
10	65	M	450	3	+	N	0	+	0	+	0	+	4 yr.	2 yr.
11	68	M	580	3	+	+	+	#	#	+	0	+	5 yr.	3 yr.
12	62	M	500	3	+	+	0	#	#	+	0	+	9 yr.	14 mo.
13	60	M	420	3	+	N	N	0	+	+	+	+	1 mo.	1 mo.
14	63	M	520	3	+	0	0	0	0	0	0	0	1 yr.	1 yr.
15	63	M	620	3	N	+	0	+	0	+	+	0	2½ yr.	2 yr.
16	55	M	860*	3	0	+	+	0	0	0	0	0	2½ yr.	2 yr.
17	59	M	500	3	N	N	+	+	0	+	0	+	9 yr.	2 yr.
18	58	M	530	3	0	0	+	+	0	0	0	+	14 mo.	14 mo.
19	58	M	520	3	N	N	+	+	0	0	0	0	5 yr.	2 yr.
20	55	M	490	3	+	N	+	0	+	+	0	+	3 mo.	3 mo.
21	75	M	400	3	+	+	0	+	0	0	+	0	Several yr.	6 mo.
22	56	M	Large	3	+	+	0	+	0	+	+	+	2 yr.	1½ yr.
23	64	M	520	3	0	+	+	+	0	+	0	+	2 yr.	2 yr.
24	77	M	740*	2	0	0	0	0	0	0	0	0	Few yr.	1½ yr.
25	66	M	440	2	0	0	0	0	0	0	0	0	1 yr.	4 mo.

* = Atherosclerotic aortic stenosis.
# = Myocardial fibrosis.
C.T. = Coronary thrombosis.
N = Extreme narrowing.
L.A.D. = Left anterior descending.
L.C. = Left circumflex.
R.C. = Right coronary.
1 = Slight coronary disease.
2 = Moderate coronary disease.
3 = Marked coronary disease.

in fourteen cases were above 600 grams; in five others, between 450 and 600 grams; and, in the four remaining cases (6, 7, 11, 12) 340 to 400 grams. Three of these patients were elderly women whose failure was of short duration. One (12) was a 75-year-old man whose heart weighed 400 grams and was the seat of considerable diffuse myocardial fibrosis.

It is possible that in cases in which the heart weighed 400 grams, or less, the load of the hypertension was not a major factor in the cause of congestive failure. If we exclude such cases from our series, and, in addition, the two cases (14, 20) of aortic stenosis of arteriosclerotic origin, there remain seventeen out of a total of forty-two cases (40 per cent) in which congestive failure developed without significant coronary disease.

Comparison of Patients With, and Patients Without, Hypertension.—Excluding the patients with atherosclerotic aortic stenosis and those with small hearts whose hypertension might be only a questionable factor, coronary disease was present in 95 per cent of the patients without hypertension, and in 60 per cent of those with hypertension. Actual occlusion of at least one major artery was found in 80 per cent of the patients without hypertension, and in only 38 per cent of those with hypertension. Thus, the difference in the incidence of marked coronary disease in these two groups is striking.

The incidence of myocardial infarction in both groups of cases is in accord with the above observations. In the nonhypertensive group there were infarcts in thirteen cases (65 per cent); in the hypertensive group, in ten cases (24 per cent).

DISCUSSION

The data presented indicate that congestive heart failure unassociated with hypertension or valvular disease is primarily the result of coronary insufficiency. The high incidence of coronary disease in cases of essential hypertension naturally raises questions concerning the role of this factor in hypertensive heart failure. Averbuck[1] studied this condition in cases of hypertension with and without cardiac failure, and concluded that coronary disease was the most important factor in 90 per cent of his patients. We find a much lower incidence. In spite of the high incidence of coronary disease in cases of essential hypertension,[2] patients with heart failure caused by hypertension had much less coronary disease than patients with heart failure unassociated with hypertension. This is apparently due to the fact that in cases of hypertension other causes operate to produce myocardial weakness long before coronary disease has advanced to the stage observed in patients without hypertension. A comparison of the incidence of coronary occlusion, marked coronary narrowing, and myocardial infarction in patients with, and without, hypertension shows the extent to which

TABLE III

PATIENTS WITH HYPERTENSIVE HEART DISEASE MANIFESTING CONGESTIVE FAILURE

NO.	AGE	SEX	HEART WEIGHT GM.	DEGREE COR. DIS.	VESSELS OCCLUDED			INFARCTS		ANGINA PECTORIS	CARDIAC ASTHMA	CLINICAL C.T.	DURATION OF SYMPTOMS	DURATION OF FAILURE
					L.A.D.	L.C.	R.C.	OLD	RECENT					
1	63	M	600	1	0	0	0	0	0	+	0	0	2 years	1 year
2	55	M	700	1	0	0	0	0	0	0	0	0	3 years	3 years
3	64	M	550	1	0	0	0	0	0	0	+	0	1½ yr.	1½ yr.
4	68	F	475	1	0	0	0	0	0	0	+	0	Several yr.	1 wk.
5	64	M	840	1	0	0	0	0	0	+	0	0	Several yr.	4 yr.
6	63	F	360	1	0	0	0	0	0	+	0	0	3 yr.	3 mo.
7	83	F	400	1	0	0	0	0	0	0	+	0	Few yr.	2 mo.
8	59	F	630	2	0	0	0	0	0	0	+	0	Few yr.	1 yr.
9	40	M	540	2	0	0	0	0	0	0	+	0	Few yr.	2 wk.
10	68	M	620	2	0	0	0	0	0	+	+	0	2 yr.	1 yr.
11	72	F	340	2	0	0	0	0	0	0	0	0	Few yr.	9 mo.
12	75	M	400	2	0	0	0	#	#	+	0	?+	19 yr.	1 yr.
13	71	F	520	2	0	0	0	0	0	0	0	0	4 yr.	1 yr.
14	77	M	800*	2	0	0	0	0	0	+	+	0	1 yr.	4 mo.
15	62	M	700	2	0	0	0	0	0	0	0	0	4 yr.	3 yr.
16	69	M	600	2	0	0	0	0	0	0	0	0	1 yr.	1 yr.
17	68	M	740	2	0	0	0	0	0	0	+	0	2 yr.	2 yr.
18	63	M	640	2	0	0	0	0	0	+	+	+	5 yr.	2 yr.
19	60	M	600	2	0	0	0	0	0	0	+	0	2 yr.	2 yr.
20	58	M	600*	2	0	0	0	0	0	0	+	0	1 yr.	2 mo.
21	55	M	670	2	0	0	0	0	0	0	+	0	2 yr.	1½ yr.
22	38	M	630	2	0	0	0	0	0	0	+	0	4 yr.	1 yr.
23	58	M	450	2	0	0	0	#	#	+	0	0	4 mo.	24 hours
24	43	M	650	3	+	+	0	0	0	+	+	+	4 mo.	3 mo.
25	59	M	610	3	+	+	+	0	0	+	0	+	9 yr.	1 mo.
26	52	M	880	3	+	0	0	0	+	+	0	+	8 yr.	2 mo.

TABLE III—CONT'D

27	64	M	510	3	+	0	+	#	#	+	0	+	8 yr.	1 mo.
28	84	M	580	3	N	+	0	0	+	+	0	+	1 yr.	1 yr.
29	45	M	670	3	N	0	N	0	0	+	0	0	6 mo.	1 mo.
30	54	F	480	3	+	0	N	+	0	+	+	0	8 yr.	1 yr.
31	58	M	580	3	N	0	0	0	0	0	0	0	3 mo.	1 wk.
32	59	M	1000	3	N	N	N	0	0	+	+	0	10 yr.	7 yr.
33	60	F	510	3	+	+	+	0	0	+	0	+	5 yr.	1 mo.
34	65	M	700	3	+	0	0	+	0	0	0	+	Several yr.	2 mo.
35	65	M	680	3	0	+	0	+	0	0	+	0	5 yr.	3 yr.
36	63	F	540	3	N	N	N	0	0	0	+	0	5 yr.	3 yr.
37	64	M	480	3	N	N	N	0	0	0	0	0	1 yr.	3 mo.
38	69	M	600	3	+	N	N	0	+	0	+	0	2 yr.	2 wk.
39	67	M	485	3	+	+	0	+	0	0	+	0	Few yr.	1 wk.
40	67	M	520	3	+	0	0	0	0	+	+	0	2 yr.	2 mo.
41	71	M	740	3	0	0	+	0	0	0	+	+	Few yr.	2 yr.
42	73	M	600	3	0	+	+	0	0	0	0	0	2 yr.	3 mo.
43	75	M	496	3	+	0	+	+	0	+	+	0	6 mo.	1 mo.
44	73	F	460	3	N	0	0	0	0	0	0	0	Few yr.	1 mo.
45	70	M	600	3	N	0	0	0	0	+	+	0	Few yr.	1 mo.
46	83	M	590	3	N	N	0	0	0	0	0	0	Many yr.	1 mo.
47	47	M	780	3	N	0	0	0	0	0	+	0	7 yr.	6 yr.
48	74	M	600	3	+	+	0	0	+	+	+	0	Many yr.	4 yr.
49	60	F	390	3	N	0	N	#	#	+	+	+	6 yr.	1 yr.

* = Atherosclerotic aortic stenosis.
\# = Myocardial fibrosis.
C.T. = Coronary thrombosis.
N = Extreme narrowing.
3 = Marked coronary disease.
L.C. = Left circumflex.
L.A.D. = Left anterior descending.
R.C. = Right coronary.

these other factors operate. There was little or no interference with the coronary circulation in at least 40 per cent of the patients with hypertension.

Several theories have been proposed to explain the nature of heart failure in patients who do not have an appreciable degree of coronary disease, but the extent to which these theoretical factors operate is unknown. Impairment of oxygen diffusion through a thickened muscle fiber will lead to anoxia, and, in this way, cause myocardial weakness.[3, 4] Some clinical evidence of the existence of this phenomenon was presented in a previous communication,[5] in which it was shown that angina pectoris occurs in cases of hypertension with much less coronary disease than is found in patients without hypertension. Since available data indicate that attacks of angina pectoris are caused by cardiac anoxia, it is probable that this cause of myocardial weakness is an important one. In hypertension, however, there is the additional factor of increased cardiac work, and it is difficult to separate this from that of hypertrophy, per se. The final heart weight at necropsy is not a reliable index of the latter handicap, for heart failure itself is a stimulus to hypertrophy,[6] and the degree attained before failure sets in is obscured by the increase that follows in its course. In addition to anoxia resulting from coronary disease, cardiac hypertrophy, and increased cardiac work, direct muscle injury may play an important part in the heart failure of hypertensive origin. Eyster[7] maintains that hypertrophy itself is evidence of such injury, and there are many data to support this thesis. If so, the sequence of events leading to congestive failure in hypertensive heart disease without marked coronary disease might be as follows: increased cardiac work, direct muscle fiber injury, hypertrophy, anoxia resulting from both hypertrophy and increased cardiac work, muscle injury of anoxic origin, congestive failure, cardiac hypertrophy resulting from congestive failure, and further anoxia and muscle injury.

SUMMARY AND CONCLUSIONS

1. The anatomic changes in forty-nine patients with hypertension and twenty-five patients without hypertension, all of whom had congestive failure, were compared.

2. In the nonhypertensive (nonvalvular) group, marked coronary disease was present in twenty-three (90 per cent); occlusion of the major coronary arteries in nineteen (76 per cent); and myocardial infarcts in fourteen (56 per cent).

3. In the hypertensive group, marked coronary disease was present in twenty-six (53 per cent), coronary occlusion in sixteen (33 per cent), and infarction in ten (20 per cent).

4. Factors other than coronary disease play an important part in heart failure of hypertensive origin in at least 40 per cent of cases.

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Corrigendum

In the article entitled "Variations in Normal Precordial Electrocardiograms," by Ralph L. Shanno, M.D., which appeared in the June, 1940, issue of the Journal, the beginning of line 18, page 716, should read "to −22 mm.," instead of "to +22 mm."

Department of Clinical Reports

COMPLETE COARCTATION OF THE AORTA

A Case Report

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HISTORY.—W. Mc., a white man, 45 years of age, was admitted to the medical service of Dr. William Weinberger, at Lebanon Hospital, with symptoms of cardiac failure (viz., dyspnea, edema, and fatigability). He had had little cardiac disability until two years before admission, although he had been apprised of his cardiac disease when he was examined for the army, in 1917. In 1927, he was observed at a veterans' hospital, and there operated upon for appendicitis. He was again told of his heart disease, that his heart was enlarged, and that the vessels in his neck were pulsating. He was an athletic automobile salesman of moderate habits.

His first signs of decompensation appeared two years prior to admission. With rest in bed and other treatment, this cleared up in a few weeks, and he was able to continue his work until five months before admission, when decompensation again set in. At the same time he developed bronchopneumonia and hydrothorax, for which he was treated at a hospital. Thence he was transferred to another hospital, where roentgenologic study revealed coarctation of the aorta. He was discharged feeling fairly well, but two months later again became acutely decompensated and was admitted to the Lebanon Hospital. The patient had had syphilis for a year; ten blood Wassermann reactions had been positive, and he had received antisyphilitic treatment.

Physical Examination.—The patient was an emaciated, middle-aged man, suffering from acute dyspnea. There were marked pulsations in both supraclavicular regions, in the left infraclavicular region, under the left scapula, and between several of the ribs. There was a large artery, about one-fourth inch in diameter, coursing across the left scapula from above downward. The heart was enlarged to the left and to the right. A loud, blowing, systolic murmur was heard all over the precordium; its maximum intensity was at the left sternal border in the second intercostal space. Gallop rhythm was present. There was congestion of the lungs. The liver was felt 4 cm. below the costal margin. The spleen was also palpable. The blood pressure was 170/88 (mercury manometer) in the upper extremities, and 110/50 in the lower extremities.

Laboratory Examination.—The blood Wassermann reaction was weakly positive (one plus).

The gonococcus complement fixation was twice positive. Roentgenograms showed rather marked notchings on the under surfaces of the ribs posteriorly (Fig. 1). The arch of the aorta was small and not definitely outlined, and the descending aorta was not visualized in the left oblique position. The trachea was displaced to the right. The electrocardiogram revealed an intraventricular conduction disturbance of the arborization block type. A clinical diagnosis of coarctation of the aorta was made by one of us because of the evidence of col-

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lateral circulation. Roentgenologic examination confirmed the diagnosis. Treatment consisted of rest in bed, digitalis, etc. The patient died fifteen days following admission.

Autopsy.—Autopsy revealed a tremendously hypertrophied heart, weighing 1200 grams. The aortic valve was congenitally bicuspid and did not admit a small finger because of inrolling, thickening, and calcification. One of the cusps was covered with fresh blood clots. The aortic arch showed little atherosclerosis. The ascending aorta was moderately enlarged, and, immediately after the point at which the subclavian came off, the aorta narrowed and ended in a complete stenosis in the region of the ductus arteriosus (Fig. 2). The aorta continued distal to the occlusion, although it was somewhat narrowed. The aorta gave off very large innominate, left common carotid, and left subclavian arteries. The iliacs were very large, and took their blood supply from the superior and inferior epigastric arteries, which were direct continuations of extremely large internal mammary arteries. The ribs which were notched posteriorly could not be dissected out because of autopsy limitations. Interesting enough was the fact that there were no reverent microscopic changes, and no evidences of syphilis or rheumatic heart disease.

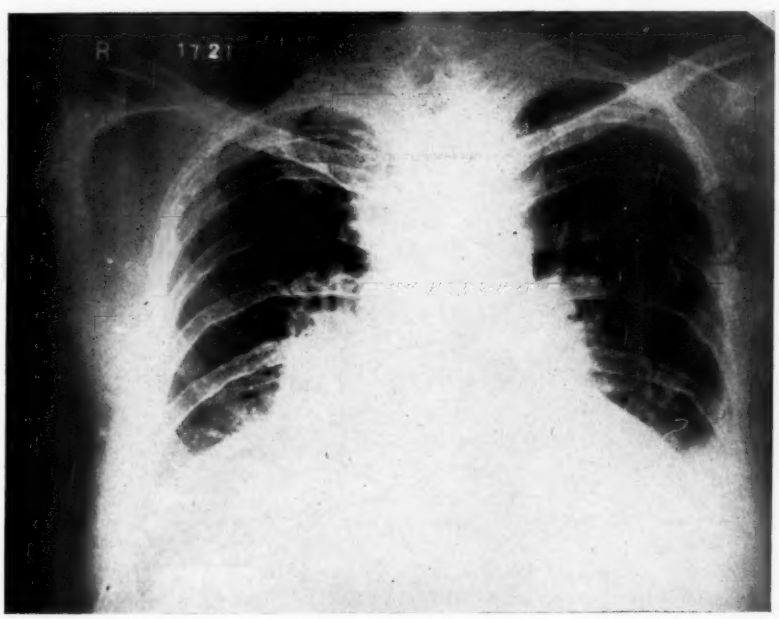

Fig. 1.—Roentgenogram showing the notchings of the inferior border of the ribs. Note widening of the aortic arch.

COMMENT

Our case is one of complete stenosis of the isthmus of the aorta. Of 200 cases of coarctation reported in the literature,[1] in only forty-seven was the stenosis complete. Further interesting features of our case were a congenitally bicuspid aortic valve and calcareous stenosis of the aortic valve of the Moenckeberg type. These anomalies are not infrequently found in conjunction with coarctation of the aorta. Maude Abbott[1] reports the presence of bicuspid valves in 25 per cent of all cases of coarctation, and in ten cases in which complete stenosis

was present. The combination of bicuspid valve and coaretation is important clinically, because there is a *locus minoris resistentiae* to the invasion of infectious processes which may predispose to a variety of conditions, such as mycotic aneurysm, aortic valvular disease, and myocardial disease. Bacterial inflammations have a predilection for the crevices of the composite cusps. This is sometimes referred to as the "commissural lesion of Lewis and Grant." In half of the cases of rupture of the aorta the aortic valve is bicuspid.

The aortic stenosis in our case is not to be considered as congenital, but rather as acquired, and, in this case, as a probable cause of heart failure. Moenckeberg stated that degenerative lesions in the aortic valve may begin at 35, almost as a physiologic process. Bishop and co-workers,[2] in their article on stenosis of a bicuspid aortic valve, note that one of the causes of aortic stenosis is a congenitally defective cusp,

Fig. 2.—Coarctation of the aorta—arrows pointing to the complete stenosis. (Note enlarged ostia of the intercostal arteries.)

with subsequent calcification. The others, of course, are of infectious origin (rheumatic and bacterial endocarditis) or are arteriosclerotic or degenerative lesions without previous inflammation.

In cases of coarctation of the aorta, the course and duration of the patient's life are wholly dependent on whether or not an adequate collateral circulation develops. There are two main routes by which a collateral circulation may establish itself; the one depends on anastomosis of the branches of the subclavian, such as the superior intercostal, postscapular, interscapular, and subscapular arteries, together with the aortic branches of the internal mammary arteries, with the first four intercostal arteries, thus carrying most of the blood into the descending aorta, and thence to the lower extremities. The second, and more circuitous, route is by anastomosis of the internal mammary arteries with the superior and inferior epigastrics, with the formation, sometimes, of tortuous, dilated vessels which often look like cirsoid aneurysms.

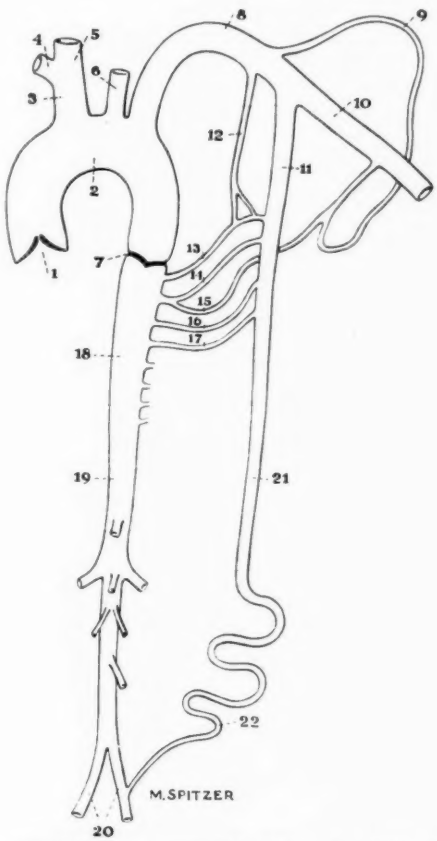

Fig. 3.—Collateral circulation. *1*, Bicuspid valve; *2*, aortic arch; *3*, innominate; *4*, right subclavian; *5*, right carotid; *6*, left common carotid; *7*, coarctation; *8*, left subclavian; *9*, subscapularis; *10*, axillary; *11*, internal mammary; *12-17*, intercostal arteries connecting with aortic intercostals; *18*, descending aorta; *19*, abdominal aorta; *20*, iliacs; *21*, superior epigastric; *22*, inferior epigastric.

In the first case, the circulation is more perfect and constant, so much so that in some instances there is no difference in pulse volume and blood pressure between the upper and lower extremities. Differences in circulation time, as demonstrated by Blumgart[3] et al., may lead to the correct diagnosis. The second, more circuitous, route is less constant and less adequate in supplying blood to the lower extremities. In this type, differences of blood pressure and circulation times between the two extremities are noted. The accompanying schema illustrates the type of collateral circulation in our case (Fig. 3).

SUMMARY

This is a case of a complete coaretation of the aorta, together with a bicuspid aortic valve and aortic stenosis of the Moenckeberg type. The history indicated that the collateral circulation had been perfectly adequate, despite the complete coaretation of the aorta. Actual impairment of the aortic outflow did not occur until after the development of stenosis of the aortic valve.

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3. Blumgart, H. L., Lawrence, J. S., and Ernstene, A. C.: The Dynamics of the Circulation in Coaretation of the Aorta of the Adult Type, Arch. Int. Med. **47**: 816, 1931.

PAROXYSMAL TACHYCARDIA IN A CHILD, TREATED WITH ACETYL-BETA-METHYLCHOLINE CHLORIDE (MECHOLYL)

BERNARD J. WALSH, M.D., AND HOWARD B. SPRAGUE, M.D.
BOSTON, MASS.

THE infrequency with which paroxysmal tachycardia occurs in children is indicated by Taran and Jennings,[1] who found fifty-two cases in a review of the literature from 1892 to 1935. In this hospital (House of the Good Samaritan), it has been noted in five of a series of 1,000 patients. Although Stepp and Schliephake,[2] in 1925, used a choline substance with success in the treatment of paroxysmal tachycardia, it was not until after the work of Starr[3] that choline compounds came into frequent use. Stenhouse[4] has recorded his satisfactory experience with acetylcholin in the case of a boy, 14 years old, during an attack of paroxysmal auricular tachycardia which had persisted for four days despite pressure on the carotid sinuses, strophanthin intravenously, and increasing doses of quinidine. Von Kiss[5] terminated a protracted attack of auricular tachycardia with acetylcholin bromide (Tonocholin B) in the case of a 16-year-old girl. This patient had previously had many attacks which were invariably stopped by induced vomiting alone, or by the combination of quinine urethrane intramuscularly and induced vomiting. Recently, Wright[6] reported the repeated use of acetyl-beta-methylcholine chloride (Mecholyl) over a period of two years in the case of a girl, 8 years of age, during numerous attacks of paroxysmal tachycardia.

Because of the paucity of reports of favorable results from the use of acetyl-beta-methylcholine chloride in children, we have thought it worth while to present the following case. This patient is, as far as we know, the youngest of those whose paroxysmal tachycardia has been successfully treated with acetyl-beta-methylcholine chloride.

CASE REPORT

A 4-year-old boy entered the House of the Good Samaritan Dec. 9, 1937. His health had been good until three weeks before, when he developed rheumatic fever, with painful, red swelling of various joints. When he was admitted to another hospital three days after the onset of the illness, a pericardial friction rub was present, as well as murmurs indicative of rheumatic valvular disease.

When he was first seen by us, it was apparent that, although much improved, he still suffered from active rheumatic fever.

On examination, the heart was normal in size. There was a harsh systolic murmur at the cardiac apex which was unchanged by respiration, as well as a loud, blowing, diastolic murmur along the left sternal border. The abdomen was soft. The liver was not felt. The blood pressure was 100/50. The pulse was regular, and the rate was 100.

From the House of the Good Samaritan, Boston, Massachusetts.
Received for publication Sept. 14, 1939.

The corrected sedimentation rate was .28 mm. per minute (normal, .38 mm.), and the leucocyte count was 10,400.

The electrocardiogram, which was similar in all essentials to that reproduced in Fig. 1, showed normal rhythm, a rate of 110, and a P-R interval of 0.13 second.

The diagnosis was rheumatic fever and rheumatic heart disease with mitral and aortic regurgitation.

Ten days after entrance an exacerbation of the rheumatic fever developed; this attack gradually subsided during the next three months. In April, 1938, a severe flare-up of the rheumatic infection began a few days after the onset of an acute upper respiratory infection. A gradual increase in the size of the heart gave evidence of further cardiac involvement. Convalescence was slow, but definite. By the early part of November, 1938, he was free of all signs of active

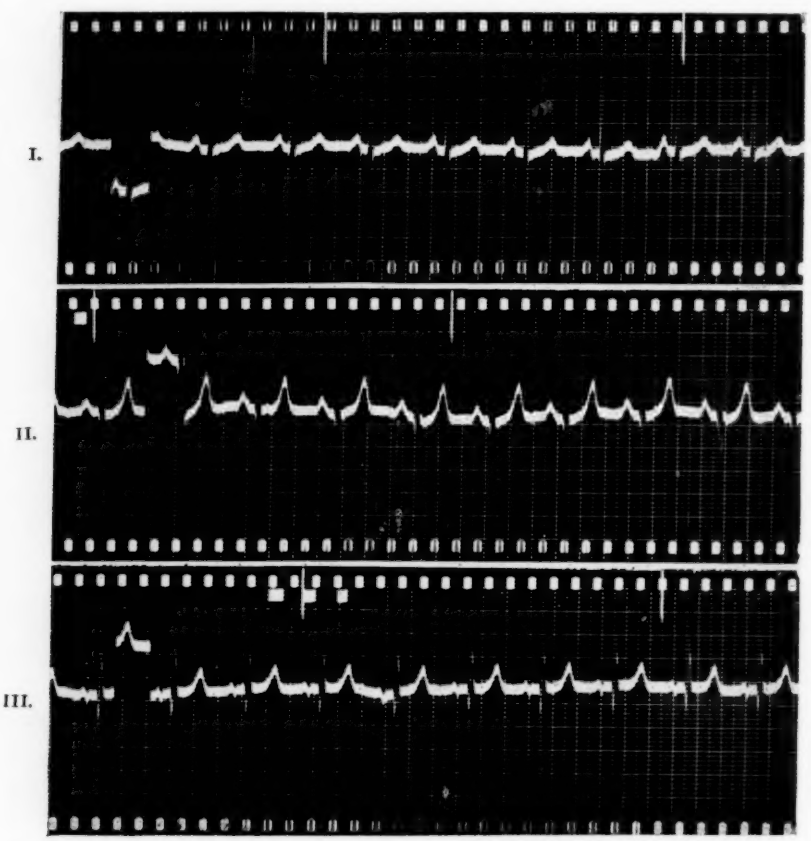

Fig. 1.—Electrocardiogram (April 24, 1939), showing normal rhythm, rate 100, Leads I, II, and III.

infection. However, during the third week of that month rheumatic fever again became manifest. A mitral diastolic murmur appeared, and the intensity of the previously described aortic murmur was increased. Recovery from this, his fourth attack of rheumatic fever while under our observation, was progressing satisfactorily when renewed activity of the infection set in during the first week of May, 1939. This was manifested by fever, anorexia, precordial pain, a more rapid sedimentation rate, and a leucocyte count of 22,000. Congestive failure

ensued in a few days, with enlargement of the liver and slight generalized edema. Aspirin and diuretin (theobromine sodium salicylate) were given, each in doses of 45 grains daily, to control the fever and promote the loss of edema. On the fifth day (May 20, 1939) after the onset of congestive failure, his heart rate rose abruptly to 240 per minute. There was no particular complaint except of pain in the right upper quadrant caused by the tender liver, the edge of which was felt 3 cm. below the level of the previous day.

The electrocardiogram (Fig. 2, Strip 1) showed ectopic auricular tachycardia, with a rate of 240 per minute. Pressure on the carotid sinus and eyeballs did not

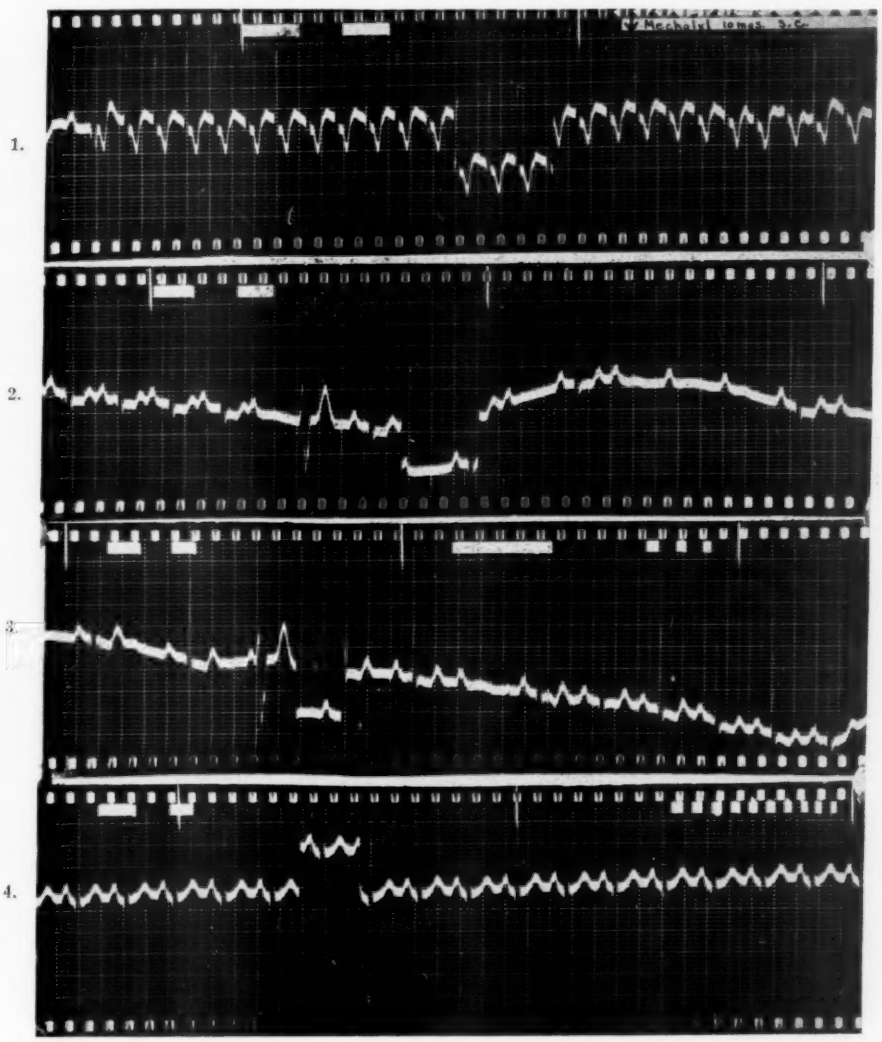

Fig. 2.—All Lead II. Strip 1. Ectopic tachycardia of supraventricular type. The exact location of the ectopic focus is probably in the lower part of the auriculoventricular node. Of interest is the isolated, normal, sinus beat shown at the beginning of the strip. Strip 2. Sinoauricular rhythm, with an auricular rate of 130 and progressive auriculoventricular block, finally resulting in a ventricular rate of thirty per minute. The fifth ventricular complex in Strip 2 represents an ectopic ventricular beat. Strip 3. Sinoauricular rhythm, with decreasing auriculoventricular block and return to 1 to 1 auriculoventricular response. Strip 4. Sinoauricular rhythm, rate 130.

alter the heart rate. Because of the rapid increase in the existing heart failure the patient's condition was precarious, with the likely prospect of a fatal termination if the tachycardia persisted. It was then decided to use Mecholyl. A single dose of 10 mg. was given subcutaneously. Within three minutes the patient flushed, then blanched, and vomited. The cardiac mechanism began to fluctuate between the tachycardia and regular beating at a rate of 90 per minute. Because of the restlessness of the patient, it was impossible to obtain an electrocardiogram during this transition period. Three to four minutes later the heartbeat became more irregular, and the ventricular rate fell to 30 per minute (Fig. 2, Strip 2). The patient lost consciousness, and, because we feared a therapeutic catastrophe, $\frac{1}{75}$ of a grain of atropine sulfate was given subcutaneously. Since there was no change during the next two minutes, $\frac{1}{100}$ of a grain of the same drug was injected intravenously. Almost immediately the heart became regular at a rate of 130, with a normal sinus mechanism (Fig. 2, end of Strip 3, Strip 4), consciousness returned promptly, and after a brief period the patient seemed entirely recovered.

It is of interest that the edge of the liver receded 3 cm. within fifteen minutes after the return to normal rhythm. For the remainder of the day the patient's condition was unchanged. Frequent observation of the heart showed that it was beating regularly at a rate of 130 per minute. However, next morning the tachycardia had returned, with a rate of 240. The electrocardiogram was identical with that shown in Fig. 2, Strip 1.

Mindful of our experience of the previous day, a dose of 5 mg. of Mecholyl was given. In five minutes the patient complained of moderately severe abdominal pain, became nauseated, and vomited. The heart rate then slowed to 70, and the beating was slightly irregular. The excursions of the electrocardiographic string shadow (observed, but not recorded) indicated a high-grade auriculoventricular block. Because of the persistence of troublesome upper abdominal pain, and of the heart block, $\frac{1}{100}$ of a grain of atropine sulfate was given subcutaneously. Three to four minutes later the heart rate became very fast (not recorded) for a few seconds, then the mechanism returned to normal. An electrocardiogram at this time showed normal sinus rhythm, with a rate of 130. To forestall, if possible, further attacks of auricular tachycardia, the patient was digitalized during the next twenty-four hours. There was no return of the ectopic rhythm.

After two days of a relatively satisfactory state, the rheumatic fever increased in severity, with evidence of further myocardial failure. The patient died May 27, 1939, seventeen months after his admission to the House of the Good Samaritan, and three weeks after the beginning of his terminal exacerbation of rheumatic fever.

COMMENT

Paroxysmal auricular tachycardia is generally of short duration and terminates spontaneously. When very rapid or long continued, congestive heart failure may appear, even in persons with otherwise normal hearts. This is caused, as Henderson[7] indicated, by the progressive shortening of diastole, which results in poor ventricular filling, lowered cardiac output, and venous stasis. The appearance of tachycardia at a rate of 240 per minute, in our patient with congestive heart failure caused by rheumatic fever, created a critical state. The treatment of such attacks has frequently been unsuccessful, but the advent of acetyl-beta-methylcholine chloride (Mecholyl) provides an additional therapeutic agent which promises to be of value, as in our case, when the

usual measures have failed. By means of this drug, the majority of those who do not respond to the usual measures (pressure over the carotid sinuses and eyeballs, induced vomiting, quinidine, digitalis, etc.) may be relieved. However, it should be emphasized that this drug is a powerful vagus stimulant, and, when given in too large a dose (as in our patient in the initial attempt to restore normal rhythm) it may cause heart block with temporary ventricular standstill. Nevertheless, there are no reported fatalities caused by acetyl-beta-methylcholine chloride, although as much as 300 milligrams have been administered[3] to an adult, with resultant transient cardiac arrest and syncope. Atropine will abolish such an effect almost immediately, and should be prepared in advance for instant use, if necessary. Although the dosage cannot be standardized (Wright[6] has found it necessary to give 100 milligrams in a single injection to a child), children, young people, and those of slight build require less than adults or those of heavy build. In young children it would seem best, in the light of our experience, to use 5 mg. first, increasing the dose in 5 to 10 mg. steps every thirty or forty-five minutes until the attack is stopped or the effects of overdosage appear.

SUMMARY

1. The case of a 5-year-old child who was seriously ill with ectopic auricular tachycardia complicating rheumatic fever, rheumatic heart disease, and congestive failure is described.

2. Normal cardiac rhythm was restored by the use of acetyl-beta-methylcholine chloride (Mecholyl).

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3. Starr, I., Jr.: Acetyl-B-Methycholin. IV. Further Studies of the Action in Paroxysmal Tachycardia and in Certain Other Disturbances of Cardiac Rhythm, Am. J. Med. Sc. **191**: 210, 1936.
4. Stenhouse, A. B.: Paroxysmal Tachycardia Treated With Acetylcholine, Lancet **2**: 1291, 1935.
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Department of Reviews and Abstracts

Selected Abstracts

Graybiel, Ashton: Diseases of the Heart: A Review of Significant Contributions Made During 1939. Arch. Int. Med. **65**: 1053, 1940.

A survey of the literature on cardiovascular disease for the year 1939 reveals much that is of interest and importance. The most notable contributions are in regard to congenital heart disease, essential hypertension and the treatment of subacute bacterial endocarditis. Consequently, these subjects have been reviewed in considerable detail.

This review is the annual one similar to the previous several years. It is an essential part of cardiac literature.

AUTHOR.

Ogden, Eric, Brown, Lewis T., and Page, Ernest W.: The Increased Sensitivity of Arterial Muscle in the Prehypertensive Phase of Experimental Renal Hypertension. Am. J. Physiol. **129**: 560, 1940.

Renal hypertensive rabbits were found to be markedly more sensitive to the pressor action of pitressin than they had been before partial constriction of the renal arteries. Similar control operations gave negative results. Hypersensitivity to pitressin was a phenomenon of the prehypertensive or early hypertensive phase. The hypertensive animals also appeared to have an abnormal pressor response to noise and fright. Although the latter stimuli operate through the nervous system, the hypersensitivity to a muscle stimulant, pitressin, leads to the belief that renal hypertension is characterized by a generalized increase in the reactivity of the muscular coat of the arteries and that this in turn may play an essential role in the production of hypertension.

AUTHORS.

Burton, A. C., and Taylor, R. M.: A Study of the Adjustment of Peripheral Vascular Tone to the Requirements of the Regulation of Body Temperature. Am. J. Physiol. **129**: 565, 1940.

The rhythmic fluctuations of peripheral vascular tone previously described (Burton, 1939) have been examined under various conditions of heat loss in order to determine how they are modified to maintain an appropriate value for the average peripheral blood flow. The pulsation of the finger volume with each heart beat has been used as an index of general peripheral vascular tone.

Those constrictions which occur in response to external stimuli or are of "psychic" origin may be distinguished from "spontaneous" constrictions by the simultaneous recording of the psycho-galvanic reflex since this, which is an index of sweat gland activity, accompanies only those vasoconstrictions which are of the former type. Otherwise, the intermittent activity in the sympathetic nerves to blood vessels is completely independent of that in the nerves to sweat glands in the palm.

The regularity of the rhythm of spontaneous vasoconstriction has been examined by statistical methods. The interval between constrictions in the

"comfortable" range of environmental temperature is between 30 seconds and 2 minutes with an average interval of 50 to 60 seconds.

As the temperature of the environment is raised, the average interval increases, as more of the longer intervals between constrictions occur.

When the subject is immersed in a well-stirred water bath of constant temperature, the rhythm of vasoconstriction is essentially similar to that found in air. This means that the intermittence of tone cannot be due to a corresponding intermittence of skin temperature. The latter is shown to have so great a thermal lag that such an origin of the intermittence would be very improbable.

The average size of pulsation in the finger, calculated for five-minute periods in the bath experiments, is remarkably constant in spite of wide variation within such a period. The changes in the level of the average size of pulsation and in the average interval between vasoconstrictions, with rising temperature of the water, have been determined. The efficiency of the modification of the rhythmical fluctuations by temperature regulation is demonstrated.

For a given environmental temperature the amplitude of the fluctuations is very similar in normal subjects. In the range of blood flow from 40 to 60 c.c./min./100 c.c. of tissue, it is maximal, with a standard deviation of ±30 per cent.

It is concluded that the reflex adjustment of the blood flow in peripheral vessels, in accordance with the requirements of temperature regulation, is a continuous process which consists in the modification of a vascular tone which is intrinsically rhythmical in character.

AUTHORS.

Jeffers, William A., Lindauer, M. August, Twaddle, Paul H., and Wolferth, Charles C.: Experimental Hypertension in Nephrectomized Parabiotic Rats. Am. J. Med. Sc. **199**: 815, 1940.

Totally nephrectomized rats will survive in parabiosis for two to ninety days following the second nephrectomy. They will show progressive weight loss and azotemia in the last week of life. Terminally hypervolemia and hypertension will usually appear. The probable mechanism of this type of experimental hypertension is discussed.

AUTHORS.

Grimson, K. S., and Shen, T. C. R.: Influence of Benzedrine, N-Methyl-Tetrahydro-Isoquinoline, Histamine, Peptone, and Anaphylactic Shock Upon the Carotid Sinus Vasomotor Reflexes. Arch. internat. de pharmacodyn. et de therap. **62**: 474, 1940.

Phenylaminopropane phosphate (Benzedrine) in small doses produces no alteration of blood pressure or of proprioceptive vasomotor carotid sinus reflexes. Larger doses increase the blood pressure and decrease the vasomotor reflexes by decreasing depressor responses. High doses abolish the vasomotor reflexes of carotid sinus origin.

N-methyl-tetrahydro-isoquinoline may decrease or reverse the hypertensive action of adrenaline without appreciably altering proprioceptive vasomotor reflexes of carotid sinus origin. Larger doses abolish these vasomotor reflexes.

Histamine and peptone in small doses increase the depressor proprioceptive vasomotor carotid sinus reflexes without altering general blood pressure. Larger doses lower blood pressure and greatly decrease the proprioceptive vasopressor and vasodepressor reflexes of carotid sinus origin.

Anaphylactic shock greatly lowers blood pressure and decreases or suppresses proprioceptive vasomotor reflexes of carotid sinus origin.

AUTHORS.

Grimson, K. S., and Shen, T. C. R.: Vasomotor Responses to Adrenaline and to Carotid Sinus Impulses in Normal, Skinned, and Denervated Legs. Arch. internat. de pharmacodyn. et de therap. 63: 95, 1939.

Our studies on the vasomotor responses of normal and skinned limbs, by using the three manometers method of Nolf or by a strohmuhr, show that vasoconstriction and vasodilatation produced by carotid sinus reflexes, direct sympathetic stimulation, and the direct injection of varying doses of adrenaline occur equally well in the normal and in the skinned limb when proper measures are taken to keep the latter warm and moist. These facts thus show that blood vessels of skeletal muscles may also react to vasomotor impulses and adrenaline injections by vasoconstriction and vasodilatation.

AUTHORS.

Shen, T. C. R., and Marri, R.: Further Studies on Cardio-Ventricular Fibrillation. A. Influence of diethylaminoethoxy-2-diphenyl (F. 1262), corynanthine and p. oxyphenyl-ethanol-methyl-amine (sympatol) on the benzol-adrenaline cardio-ventricular fibrillation in the dog. B. The Role of the Hypertensive Action of Adrenaline. Arch. internat. de pharmacodyn. et de therap. 64: 58, 1940.

Simultaneous injection of diethylamino-ethoxy-2-diphenyl (F. 1262) and adrenalin produces an arterial hypotension and prevents the benzol-adrenaline cardioventricular fibrillation. Five to sixty minutes later injection of adrenalin alone produces an arterial hypertension and subsequent death of the benzol-inhaling dog by ventricular fibrillation.

Intravenous injection of corynanthine (0.5 to 2 mg. per kg.) induces a prolonged fall of arterial blood pressure, lasting decrease of the carotid sinus vasomotor reflexes and a decrease of the hypertensive action of adrenalin as well as a protective action upon the benzol-adrenaline cardioventricular fibrillation.

Five to ten mg. of p-oxyphenyl-ethanol-methyl-amine (sympatol) intravenously injected either before or together with adrenalin scarcely protects the benzol-inhaling dogs against ventricular fibrillation.

Intrapericardial injection of 0.2 mg. of adrenalin per kg. into a benzol-inhaling dog produces a progressive rise of arterial blood pressure but provokes no ventricular fibrillation. Intravenous injection of 0.02 Gm. of adrenalin per kg. produces an abrupt elevation of the arterial blood pressure and death by ventricular fibrillation.

The role of adrenalin itself and the arterial hypertension induced by adrenalin in determining the production of the benzol-adrenalin cardioventricular fibrillation is discussed. The characteristic form of the rise of blood pressure which produces the ventricular fibrillation of the chloroform or benzol-adrenalin type is pointed out.

AUTHORS.

Bouckaert, J. J., Grimson, K. S., and Heymans, C.: Increase of Blood Pressure by Perfusion of the Ischaemic Kidneys of Hypertensive Dogs. J. Physiol. 96: 10, 1939.

These experiments show that, under certain experimental conditions, the incorporation of the kidneys of a renal-ischemia hypertensive dog into the circulation of another normal dog will produce an elevation of blood pressure.

In order to be able to induce a sustained high blood pressure, the liberation of this not very active vasopressor renal factor must, however, be associated

with either a primary or a secondary disturbance of the physiologic, under normal conditions very effective, mechanisms of the proprioceptive homoeostatic blood pressure regulation.

AUTHORS.

Adams, W. E., and Escudero, Lucilo: Disturbances in the Circulation and Respiration in Obstruction of the Blood Flow to and From the Heart. Surg. Gynec. and Obst. **70**: 744, 1940.

Obstruction of the blood flow through vessels leading to or from the heart was produced in dogs. The resultant variations in cardio-circulatory and respiratory physiology simulated very closely those usually associated with certain clinic conditions. Of the large blood vessels connected with the heart, obstruction of the venae cavae and azygos were by far the best tolerated. Cardiac activity remained regular for as long as nine minutes with complete cessation of blood flow to the right heart. Obstruction of the pulmonary artery was tolerated the poorest of that of all the great vessels of the heart, presumably because of the opposite factor, that is, in vena caval obstruction the cardiac muscle is put somewhat at rest whereas in obstruction of the pulmonary artery the right heart burden is greatly increased. The practical application of these findings to clinical problems in thoracic surgery is discussed.

AUTHORS.

Holman, Emile: Hemicardiac Hypertrophy Due to Increased Peripheral Resistance. A Study of Pulmonic and Aortic Stenosis Experimentally Produced. J. Thoracic Surg. **9**: 262, 1940.

Aortic stenosis was produced in three very young animals, resulting in marked hypertrophy of the left ventricle without dilatation of the ventricular cavity.

Pulmonic stenosis was produced in two very young animals, resulting in marked hypertrophy of the right ventricle without dilatation of the ventricular cavity.

Hemicardiac hypertrophy under these two conditions is due to an increased resistance, unaccompanied by ventricular dilatation. This is in marked contrast to the cardiac enlargement seen in the presence of a large arteriovenous fistula, which is preponderantly due to a dilatation and only in slightest degree to an hypertrophy. In the presence of a fistula there are a decrease in peripheral resistance at the site of the fistula and an increase in cardiac output, the extent of these changes being dependent upon the size of the fistula.

Cardiac enlargement observed clinically or radiographically, therefore, may be due either to dilatation or to hypertrophy. It is inaccurate to refer to such enlargement as "cardiac hypertrophy" until proved by direct observation of the heart.

AUTHOR.

DeWesselow, O. L. V. S., and Thomson, W. A. R.: A Study of Some Serum Electrolytes in Hypertension. Quart. J. Med. **7**: 361, 1939.

The serum of patients suffering from essential and malignant hypertension tends to show a lower level of potassium than that of patients with a normal blood pressure on the same diet; this is especially marked in malignant hypertension.

Low levels of serum-sodium are not infrequent in malignant hypertension. Administration of sodium salts raises the blood pressure of hypertensive sub-

jects, while potassium salts have the opposite effect. These alterations are slight, and the amounts of the salts required to produce them are unlikely to be taken in a freely chosen diet.

Attempts at depletion of the body sodium were without effect on the blood pressure.

AUTHORS.

Thomson, William A. R.: Acetylcholine and Potassium in Relation to Cardiac Function. St. Thomas's Hosp. Rep. 4: 59, 1939.

The effect of acetyl-beta-methylcholine chloride (mecholyl) upon the electrocardiogram and the serum potassium was investigated in seven individuals in whom no abnormality of the cardiovascular system could be detected.

The changes observed in the electrocardiogram consisted of tachycardia, accompanied or followed by sinus irregularity or varying degrees of auriculoventricular heart block. Following the tachycardia, the heart rate usually became considerably slower than the control rate. During the period of tachycardia the height of the T wave was usually diminished and frequently during the subsequent period of slowing T became higher than in the control record.

Following the injection of mecholyl, significant changes in the level of the serum potassium occurred in only two patients, and on both occasions the increase was accompanied by a definite slowing of the heart rate and an increase in the height of the T wave. In the other five patients the effect of the mecholyl had either practically passed off or had not yet begun at the time when blood was withdrawn for the estimation of the potassium.

The bearing of these preliminary observations on the question of the relationship of acetylcholine, potassium, and the digitalis group in their action on the heart is discussed.

AUTHOR.

Cossio, P., Aubone, A. Castro, and Marra, y R. R.: Cardiovascular Tomography. Rev. argent. de cardiol. 6: 209, 1939.

1. Left Auricle and pulmonary veins.

The authors have analyzed the tomographies of normal subjects and of thirty-five patients with mitral disease (mitral stenosis, mitral stenosis with insufficiency, and mitral stenosis with aortic insufficiency). In normal cases the tomographies clearly show the right and left pulmonary veins which can both be followed through the projection of the cardiac shadow. In 70 per cent of the cases with mitral disease the right and left pulmonary veins are also well visualized, as well as the left auricle with both its borders, right and left. The left border is well identified because of the easy visualization of the left pulmonary veins. The trachea and its bifurcation are also made perfectly visible, this making the injection of lipiodol unnecessary for this purpose. In cases in which the right border of the heart shadow is formed by a very dilated left auricle, it is possible to identify through this shadow the right border of the right auricle.

The authors point out that apart from the valuable information obtained by this method in mitral disease, the identification of the pulmonary veins is of importance because: 1) it allows the recognition of their topography in vivo; 2) in doing so, difficulties and errors of interpretation in tomography of the lungs may be avoided; 3) by the identification of the left pulmonary veins the left border of the left auricle is easily recognized.

AUTHORS.

Boyd, Linn J., and Scherf, David: The Electrocardiogram After Mechanical Injury of the Inner Surface of the Heart. Bull. New York Medical College 3: 1, 1940.

In seventeen experiments mechanical irritation (scratching) of the endocardium and of the adjacent myocardium at the apex of the dog heart in situ did not cause a high or low take-off of the final deflection, as seen after similar irritation of the outer layers of the myocardium in the same region. Changes in the form of the T waves and a depression of the S-T segment alone occur. The alterations disappear within a few minutes.

AUTHORS.

Boyd, Linn J., and Scherf, David: The Electrocardiogram in Experimental Pericardial (Epicardial) Injury. Bull. New York Medical College 2: 168, 1940.

Mechanical irritation of the surface of the heart (light blows, pinching, rubbing with sandpaper) at circumscribed areas produces a high take-off of the terminal deflection.

The same alterations develop after concentrated salt solutions and other irritating substances are brushed upon the surface of the heart.

The alterations in the electrocardiogram appear in a few seconds, immediately reach their acme, and decline in a few minutes. The initial deflection remains unaltered. The high take-off is always present in Leads II and III regardless of whether an area on the surface of the left ventricle or the apex of the right is irritated. The alterations of the S-T segment in Lead I upon irritation of the right ventricle consist in a low take-off. The alterations in Lead I after irritation of various areas of the left ventricle do not permit the recognition of any regularity. No electrocardiographic alterations could be obtained from the anterior wall of the right ventricle.

The upward displacement of the S-T segments by a high take-off shortens the S wave in Leads II and III after division of the right bundle branch and can even prevent its appearance. In the presence of a high take-off the typical alterations of the final deflection do not appear after faradic stimulation of the stellate ganglion. However the width of the ventricular complex is markedly diminished.

Isolation of the irritated area from the neighboring tissues diminishes the high take-off considerably or abolishes it.

The alterations of the S-T segment are explained by the admixture of a monophasic current of injury to the electrocardiogram. In addition to the size of the irritated place its contact with the neighboring tissues and apparently also their configuration is decisive for the degree of this admixture. The theory of participation of reflexes or vascular spasm is rejected.

AUTHORS.

Robinson, Samuel C., and Brucer, Marshall: Hypertension, Body Build and Obesity. Am. J. Med. Sc. **199:** 819, 1940.

The role of obesity in hypertension is here evaluated by separating obesity from the body build factor with which it is intimately bound.

Obesity is found to be intimately linked to the lateral or broad build type; it occurs infrequently in linear or slender build men and women. Of broad-chested men 37 per cent are heavyweight, whereas only 3 per cent of slender men are heavyweight.

Body build is shown to be closely correlated with hypertension. In any weight group the broad-chested individuals show the highest mean systolic and diastolic pressures, the greatest incidence of hypertension, and the lowest incidence of low blood pressures.

When the build groups are held constant obesity shows an uncertain correlation with hypertension. In those instances where a positive correlation to blood pressure is demonstrated, it is strikingly less significant than the build correlations in nearly every instance.

Obesity shows its greatest correlation to blood pressure in the linear or slender build groups. In the lateral or broad groups no correlation is noted; sometimes there is a reversal of the expected trend.

Therefore, body build is the true genotypic factor which, regardless of his weight, determines in a great measure the predisposition of any individual to hypertension.

The role of obesity in hypertension is found to be small. The current widely accepted role of obesity must be revaluated.

AUTHORS.

Matthews, Edward, and Wood, W. Barry, Jr.: Cardiac Arrhythmia During Cheyne-Stokes Respiration. Bull. Johns Hopkins Hosp. **66**: 335, 1940.

Four cases of cardiac failure exhibiting marked arrhythmia of the heart during the phases of Cheyne-Stokes respiration were studied. Simultaneous electrocardiographic and respiratory records were obtained through the entire Cheyne-Stokes cycle in each case. In three of the cases, bradycardia began in late apnea and continued till the latter half of hyperpnea and persisted till late apnea. In one case, in which initial P-R interval was 0.32 second, the bradycardia was due to complete auriculoventricular block. In the other three cases the bradycardia was sinus in type, although in two of the three there were changes in the P waves, suggesting shift in the pacemaker.

Two of the patients had received no digitalis prior to the occurrence of the phenomenon. In the two cases in which it was tested, atropine abolished the arrhythmia without affecting the periodic breathing. Carotid sinus pressure was applied during apnea in two cases and changes in the cardiac mechanism similar to those occurring spontaneously in hyperpnea were produced. In one case, voluntary hyperpnea during a period of apnea provoked a transient alteration in cardiac mechanism. No studies of the arterial blood gases were made.

The reports of previous similar cases are reviewed and possible explanations of the arrhythmia are discussed.

AUTHORS.

Klainer, Max J.: The Prognostic Significance of Right Axis Deviation in Arteriosclerotic and Hypertensive Heart Disease. Am. J. Med. Sc. **199**: 795, 1940.

Right axis deviation may occur in hypertensive and arteriosclerotic heart disease, even in the presence of left ventricular hypertrophy.

It is commonly associated with recent attacks of coronary thrombosis and with severe myocardial damage. In thirteen autopsied cases myocardial infarcts were found in ten and diffuse fibrosis in two. Right axis deviation occurs in cases with anterior or posterior infarction singly or in combination.

Of the patients with right axis deviation in whom follow-up studies were made, 83 per cent died within twenty-seven months and 43 per cent of the total series died within one month of its discovery. The occurrence of right axis deviation in patients with hypertensive or arteriosclerotic heart disease without rheumatic and congenital heart disease or cor pulmonale indicates a poor prognosis.

Another mechanism altering the electrical axis of the heart may be widespread necrosis of one ventricle which can completely nullify the effects of hypertrophy of that ventricle.

AUTHOR.

Walzer, Leo: Incidence of Auricular Fibrillation in Mitral Stenosis With Congestive Failure. Ohio State M. J. **36**: 281, 1940.

Sixty-nine patients with congestive failure, having mitral stenosis as the predominant cardiac lesion and selected from 309 consecutive patients admitted to Lakeside Hospital with the diagnosis of mitral stenosis, form the basis of this report.

Auricular fibrillation occurs with increasing regularity in the congestive failure of mitral stenosis with increase in age. Seventy-eight per cent of the patients in this series had auricular fibrillation. The chief exception to the concurrence of congestive failure and auricular fibrillation in mitral stenosis was the congestive failure of children and adolescents. Here the congestive failure was a part of the picture of active rheumatic infection.

Auricular fibrillation is to be expected in the congestive failure of mitral stenosis. Its absence warrants an intensive search for evidence of active rheumatic infection. If none is found one should suspect either that mitral stenosis is not present, or, if present, is not the important cardiac lesion.

AUTHOR.

Rosenberg, David H.: Fusion Beats. A Report of a Clinical Instance and an Experimental Study in the Dog. J. Lab. & Clin. Med. **25**: 919, 1940.

A clinical case manifesting an ectopic, ventricular, parasystolic rhythm with various degrees of fusion with the normal sinus impulse is recorded. The mechanism involved in the production of fusion beats is demonstrated experimentally in the dog. Attention is directed to the importance of recognizing fusion beats in the electrocardiogram.

AUTHOR.

Gross, Harry: Water Content of the Myocardium in Hypertrophy and Chronic Congestive Failure. J. Lab. & Clin. Med. **25**: 899, 1940.

The water content of the myocardium from persons with cardiac hypertrophy and with cardiac hypertrophy with congestive heart failure was determined and compared with that of normal persons used as controls.

The hearts from patients with wasting diseases and from aged persons showed relatively low water contents. Children, on the other hand, showed relatively high myocardial water contents normally and in congestive heart failure.

In cardiac hypertrophy without failure, the water content was not increased. The increase in heart weight in cardiac hypertrophy is due to an intrinsic increase in muscle mass and not to an increased amount of water.

In congestive heart failure the water content of the myocardium was increased due to anasarca which also involved the myocardium. The greatest increase of water was observed in childhood, reaching 82.1 per cent in one instance. Normal figures in the aged patients with wasting diseases may represent actual water retention.

The beneficial effects of diuresis in congestive heart failure may, in part, be due to reduction of excessive myocardial water content, thereby improving cardiac contractility.

AUTHOR.

Luten, Drew, and Wedig, John H.: The Incompatibility Between Congestive Heart Failure and Angina Pectoris. J. Missouri M. A. **37**: 96, 1940.

That there is a certain incompatibility between angina pectoris and heart failure is well recognized. It is suggested that this incompatibility may be re-

lated to cardiac tone. Competent study of certain antagonistic factors in these syndromes might possibly throw further light on the precise mechanism involved in the production of angina pectoris.

AUTHORS.

Wright, Irving: Conservative Treatment of Occlusive Arterial Disease. Arch. Surg. **40**: 163, 1940.

An attempt has been made to review and evaluate the more important of the methods used in conservative treatment of occlusive peripheral vascular disease, especially arteriosclerosis obliterans and thromboangiitis obliterans. The more general use of the conservative approach definitely affects the statistics on amputations. It should be recognized that it is far better surgery to take meticulous care of small lesions and produce healing than to perform major amputations. In a series of 100 consecutive cases of thromboangiitis obliterans studied since 1931 by Littauer and me, only three major amputations were performed, all on persons who would not stop smoking. Most of the patients have been followed for from two to eight years. The incidence of amputation in this group may be expected to rise with the trauma and other factors incident to the passage of time, but it is extremely doubtful that the former amputation rate of from 40 to 50 per cent will again be observed. For arteriosclerosis obliterans, our figures are not so encouraging. We have not yet compiled statistics on this condition, but we have been impressed by its more hesitant response to therapy. On the other hand, an increasing number of patients who have been advised to submit to amputation are today walking on the condemned leg as a result of conservative therapy. Continued study may result in greater success in this regard. Amputation must be regarded as an admission of defeat, an acknowledgment of the physician's inability to solve the problem with which he is confronted.

It is important that the recent trend in certain quarters toward submitting all patients with vascular disease to the same form of therapy, whether it be use of the pressure suction boot, administration of hypertonic saline solution, or intravenous administration of typhoid vaccine, be discouraged. The problems presented by different diseases and by different patients with the same disease are more frequently unlike than identical. Each should be given individual consideration before the therapeutic regimen is instituted. It is also of vital importance that the conception that peripheral vascular disease is purely local, involving only the extremities, be overcome. Each patient should be submitted to a complete study in order that evidences of vascular damage anywhere in the body may be discovered and proper therapy instituted. For example, it is not yet generally recognized that thromboangiitis obliterans may affect any artery in the body.

AUTHOR.

Homans, John: Lymphedema of the Limbs. Arch. Surg. **40**: 232, 1940.

An attempt has been made to sort out and describe the lymphedemas, especially of the lower limbs, which are due to local causes. The elephantiases, that is, those associated with a total disappearance of the lymph vessels, are unexplainable, and, as one might suppose, they are really incurable; that is to say, there is no way of restoring drainage of the tissue fluids. To do away with the swelling, one must remove the tissue in which fluid collects. This need not, as a rule, be done for the thigh. It is enough to reduce the size of the leg below the knee.

None of the other lymphedemas are wholly of lymphatic origin. Those which originate in femoroiliac thrombophlebitis are certainly due in part to involvement

of the larger lymph vessels of the pelvic brim in the perivascular exudate which is so often present in these cases, but venous obstruction (at first) and peripheral vasospasm (later) certainly contribute to the swelling of the limb.

The allergic edemas undoubtedly are going to prove of increasing clinical importance. As yet, it is not known whether such states can become established without definite acute attacks of redness, swelling, and fever. If edemas of this sort can arise quietly, as it were, then the various fungi of the skin must be even more common and have more access to the internal mechanism than is now believed to be the case. Without proposing to be an alarmist, I deprecate the rather general tendency of members of the medical profession to shut their minds to this matter.

The reflex edemas, that is, the rare and picturesque swellings which arise unpredictably from trivial injuries and infections, seem to be related to sympathetic control of the peripheral blood vessels. However, their peculiar mode of origin, especially in trauma to certain nerves (the median and sciatic) should make one careful not to be too certain of their nature, and the hypersensitiveness to touch which is so often associated with them appears to give them a relation to the causalgias. There is much to be learned of the relation of pain, superficial tenderness, and edema, as a complex, to the somatic and sympathetic nervous systems. The reflex pathways concerned with the reflex edemas and causalgia-like states require especial study.

AUTHOR.

deTakáts, Géza, and Reynolds, John T.: Amputation for Peripheral Vascular Disease. Arch. Surg. **40**: 253, 1940.

The indications for amputation and the methods and results of amputations done in certain cases of peripheral vascular disease have been discussed. Determination of the proper level of amputation and preparation of the patient are described. Factors decreasing mortality are emphasized. The study was based upon fifty major amputations. Although a mutilating operation, amputation for vascular disease continues to rehabilitate economically handicapped or seriously endangered patients for whom conservative measures are ineffective. The mortality can be reduced to a small, unavoidable percentage, especially by amputation before infection is superimposed on gangrene.

AUTHORS.

Shohet, Allan S., Taub, Samuel J., and Kupersmith, Harry: Studies in Coronary Disease: I. Relation of Coronary Sclerosis to Heart Weight and to Right and Left Ventricular Hypertrophy. Illinois M. J. **77**: 240, 1940.

This study is based upon a critical review of 7,970 consecutive autopsies performed at the Cook County Hospital, and is a part of a larger work on the nature and manifestation of coronary disease. Among these, there were 305 cases of proved coronary disease, and of these, 183 cases were discarded because of the presence also of possible noncoronary factors in cardiac hypertrophy, such as hypertension, valvular lesions, syphilis, myocardial inflammatory lesions, pericarditis, thyroid disease, congenital heart disease, anemias, cor pulmonale, and impaired kidney function.

A study of the 122 cases of exclusive coronary disease reveals the unquestionable effect of coronary disease per se on cardiac hypertrophy. The graphs also show a hitherto unrevealed and totally unsuspected reciprocal relationship between the two ventricles and the intensification of the disease of the coronary arteries. It appears that early in the course of the disease both ventricles hypertrophy to an approximately equal degree of their original thickness. However, with an in-

crease in the degree of coronary sclerosis, the left ventricle continues to grow in thickness, while the right ventricle actually appears to lose in thickness until such a time when the sclerosis of the arteries becomes very severe. When this stage is reached, the roles seem to reverse. The left ventricle then thins out somewhat and the right ventricle resumes its progressive hypertrophy. No explanation is offered for this phenomenon.

AUTHORS.

Theis, Frank V., and Freeland, M. R.: Thromboangiitis Obliterans. Treatment With Sodium Tetrathionate and Sodium Thiosulfate. Arch. Surg. 40: 190, 1940.

Intravenous injections of sodium tetrathionate and sodium thiosulfate were usually followed by increased peripheral temperatures, decreased pulse rate, and reduction in blood pressure. These physiologic responses were associated with changes in the oxygen capacity and in the oxygen saturation of the arterial and the venous blood.

These effects were opposite to those that occurred with smoking, which is an important etiological factor in thromboangiitis obliterans. The therapeutic value of sodium thiosulfate and sodium tetrathionate is probably due to the changes produced in the blood and the resulting physiologic responses.

AUTHORS.

Ochsner, Alton, and DeBakey, Michael: Therapy of Phlebothrombosis and Thrombophlebitis. Arch. Surg. 40: 208, 1940.

The therapy of thrombophlebitis is reviewed and is classified into prophylactic, conservative, and radical measures.

The prophylactic measures consist of hydration, mobilization, respiratory stimulation, prevention of increased abdominal tension, application of heat, administration of sodium thiosulfate, hirudinization, and heparinization.

The conservative measures consist of immobilization and elevation of the involved extremity, application of heat, hirudinization, use of compression bandages, and production of vasodilatation.

In the authors' experience, the best therapeutic measure is procaine hydrochloride block of the regional sympathetic nerves. The rationale of this therapeutic measure is discussed, and the excellent results obtained from its employment in twenty-two cases are described. The technique of "sympathetic block" as used by the authors is described briefly and illustrated.

The radical procedures consist of ligation, excision, incision and drainage, and thrombectomy or embolectomy.

AUTHORS.

Harrison, Tinsley R.: Some General Principles in the Bedside Diagnosis of Heart Disease. South. M. J. 33: 308, 1940.

The necessity for a careful analysis of the subjective manifestations of patients with complaints referable to the cardiovascular system has been emphasized. In order to illustrate this, certain features of two symptoms have been considered. Recurrent attacks of weakness have been discussed, and four conditions which are frequently overlooked have been mentioned as common causes of the complaint. These conditions are: (1) sudden change from the recumbent to the upright position; (2) carotid sinus syncope; (3) spontaneous hypoglycemia; and (4) allergic dizziness. The fact that these conditions are usually incorrectly diagnosed unless a very careful history is taken has been emphasized.

Certain aspects of another important symptom, pain in the chest, have also been discussed. It has been pointed out that the diagnosis of angina pectoris is almost entirely dependent upon an accurate history. Certain conditions such as paroxysmal tachycardia, paroxysmal auricular fibrillation, and spontaneous hypoglycemia, which may induce the attacks of angina pectoris in the absence of mental or physical exertion, have been considered. The relation of angina pectoris to chronic pain in the shoulder region has been discussed. The similarity of the pain produced by herniation of the stomach through the esophageal hiatus of the diaphragm to the pain of angina pectoris has been mentioned. Emphasis has been placed on the general principle that a careful and detailed history is usually the most important means of arriving at the correct diagnosis in a patient with a pain in the chest.

AUTHOR.

Wood, Paul: The Action of Digitalis in Heart Failure With Normal Rhythm. Brit. Heart J. 2: 132, 1940.

Digitalis effected demonstrable improvement in eighteen out of twenty cases of congestive heart failure with normal rhythm. This was judged by serial measurements of the venous blood pressure in those with systemic congestion, and of the arm-to-tongue circulation time in those with pulmonary congestion.

Since it has been stated that rheumatic heart disease responds better to digitalis than other etiological types, it is of interest that only one of the present series was rheumatic.

Observations showed that the fall in venous blood pressure following intravenous digoxin was not due to slowing of the heart.

A single observation refuted the view that the beneficial action of digitalis is due to its constricting effect upon the hepatic vein.

AUTHOR.

Weichsel, H. S.: Studies in Peripheral Vascular Diseases. I. Intravenous Calcium in Occlusive Vascular Disease. Ann. Int. Med. 13: 1150, 1940.

Weichsel reports good results in treating peripheral vascular disease with calcium. The number of patients so treated is not specified. The solution used at first was a 10 per cent calcium gluconate in 10 to 20 c.c. of saline, later 2 grams of calcium chloride in saline. The injections were given intravenously once a week for twelve weeks. The observations are based on thirty recordings of the Tycos recording oscillometer before and after treatment and in addition relief of pain, drop in blood pressure, slowing of pulse, increase in claudication distance, reduction in amount of rest, pain and night cramps, healing of ulcers, and promotion of collateral circulation.

MCGOVERN.

Baker, T. W.: Histaminase in the Treatment of Cold Allergy. J. A. M. A. 114: 1059, 1940.

This is the report of two cases of cold sensitivity successfully treated with histaminase and gradual desensitization to cold. In each instance the condition had been precipitated by the use of cold water, milk, or handling ice. The use of histaminase for other allergic conditions is suggested.

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